

Smoking, Pregnancy and Publicity

THE appearance of a news story last week opening with the statement that cigarette smoking during pregnancy "caused the deaths of 1,500 babies in Britain last year" was bound to be received by scientists with a certain cynicism that this was just another case of the heat of the media metamorphosing an author's possibility into certainty. This turned out not to be so.

The occasion for the story was the publication in *Concern*, the journal of the National Children's Bureau, of an article by Mr Harvey Goldstein. It was obvious on reading this article that Mr Goldstein was very accurately reported. And furthermore he was quoting in *Concern* his own research results, published with Professor N. R. Butler and Mr E. M. Ross in the *British Medical Journal* of April 15, 1972. In that paper the authors concluded "an estimate can be made of the potential saving in newborn lives per year if all these women [regular smokers] could be persuaded to stop smoking during pregnancy. With the 1970 overall foetal and neonatal mortality rates, this might amount to a saving of approximately 1,500 babies each year . . .". Slightly different from the *Concern* version, and a lawyer would not like the ambiguous "potential", but it is clear that the sense of the learned paper was accurately conveyed in the press.

Is their conclusion true and if true is it necessarily good to advise a pregnant mother to stop smoking?

The paper is a compilation of statistics from 17,000 births in one week in 1958 (before much publicity had been given to health risks in smoking) and 7,000 late foetal and neonatal deaths from a three-month period in the same year. Cigarette smoking is parametrized by the number smoked daily both before pregnancy and after the fourth month. An attempt is made to allow for "mediating" variables such as social class, maternal age and height and so on. Two analyses are made—one of perinatal death rates, the other of birth weight of live babies, both being functions of the two variables—number smoked before and during pregnancy.

The analyses show the following: (i) that of those who do not change their habits, the non-smokers have heavier babies which are less prone to perinatal fatalities (the death rate is 30% higher amongst heavy smokers than non-smokers); (ii) those who start smoking in pregnancy tend to have lighter babies with more fatalities; and (iii) those who stop, likewise tend to have heavier babies and less fatalities. One more feature, not mentioned by the authors, is that it seems that if five or more cigarettes are smoked daily in the latter part of pregnancy, life and weight prospects are independent of the number smoked, so cutting down to five does not improve things. The figures are clearly presented and are well worth close scrutiny; one may doubt that the populations of those who make extreme changes in habits are big enough to say very much, but the data have a general ring of credibility to them.

Alas, the authors felt constrained to draw the conclusion for health education that we have already quoted

and Mr Goldstein chooses to put it into even plainer words.

It must be said that researchers into cigarette smoking would regard this as an unsatisfactory experiment. They would want to know a lot more about the behaviour of the smoker than is given, and in particular they would be very interested in those who gave up smoking entirely during pregnancy. What had their smoking habits been like before? It must be remembered that these were in no sense controlled observations—the observer could not designate at random who was required to cut down and since this was the 1950s there were fewer social pressures on the smokers. Thus the only people who stopped were those who found it no problem to do so and could perhaps see advantages to it, such as saving money on approaching an expensive time. In other words, the social smoker who probably did not inhale, certainly not the smoker who needed cigarettes to calm nerves. Lack of control over the observations undoubtedly led to personality entering in as a variable. The woman who can give up smoking easily is a different type of person from the one who cannot, and for all we know may be less prone to perinatal fatality and light babies. There is a danger in all statistical studies in moving from parameters to the physical world—we can infer that a die is most likely biased but we cannot infer how this is actually done. We can likewise infer that those who gave up smoking on average improved their children's health prospects but we cannot, from statistics, infer how or even that smoking is the key to it.

What should the public be told? Those who can stop smoking during pregnancy should be given every encouragement. But no social pressure should be brought to bear on those who do not wish to or are unable to stop. This study has not shown that the 1,500 babies could be saved because it has not shown that compulsory abstinence produces the same sort of statistics as voluntary abstinence. In fact, the later stages of pregnancy seem no time to try to break the habit, with all the well-known tensions that usually implies. Further, there is a serious problem in hindsight publicity. It is natural that every mother who smokes, who has lost a child and who hears of this study will assume a connexion between smoking and the death in her own family, although the background of "natural" fatalities is three times bigger than the increment attributed to the smoking mother. It is not clear that it makes any psychological sense to expose her to guilt feelings.

Pregnancy is a time of heightened emotion, change in life-style (often including loss of earnings) and well-meaning advice. Mothers-to-be have always been under pressure to avoid excessive weight gains and this pressure, it is well known, frequently causes distress. Cigarettes often keep both weight and nerves under control—it is quite possible that advice to stop smoking may have exactly the wrong effect on the mother's total health.



Tracked Hovercraft—the Need to Retain Options

TRACKED Hovercraft Limited is dead and Mr Michael Heseltine's political future is in jeopardy. These are the unmistakable facts to emerge from a week full of incident following the publication of the Select Committee on Science and Technology's report on the circumstances of the closure of the National Research Development Corporation's subsidiary.

But all is not completely lost and while the corpse is still at Earith the persuasiveness of Mr Airey Neave and the showmanship of Professor Eric Laithwaite might combine, even now, to resurrect at least a part of the project.

The scientific and technological aspects of the closure of THL have in the past week unfortunately received a great deal less attention than the deeds and denials of Mr Michael Heseltine, Minister for Aerospace and Shipping. There seems little doubt that in spite of Mr Heseltine's hastily-called press conference last week to rebut the accusations of the committee, he made a grave error on February 12 by telling the House of Commons that at that time the government was still considering whether or not to provide financial assistance for THL. Nothing in the past week, even Mr Heseltine's own words, has occurred even to suggest that this statement was true. Mr Heseltine's fate, however, should not affect the future of the work in Britain on linear motors and novel means of transport.

One hopes the political element can be separated from the decision now urgently needed from the government on whether or not a national centre for linear motor work is to be set up in Britain. It must be made clear that the proposal of Professor Laithwaite and the Imperial College group for such a centre to be set up at Earith—a proposal that has been eagerly adopted by the select committee—does not in any way constitute the resetting up of Tracked Hovercraft Limited.

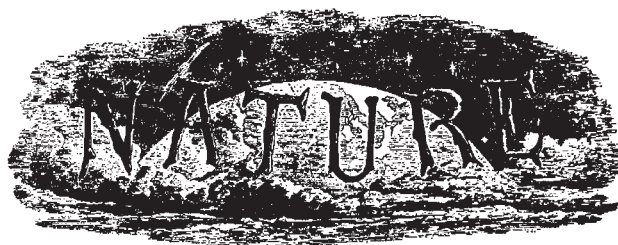
The government was right to decide that THL did not merit further financial support in order to develop the vehicle then under test. But the select committee is also right to point out that the government did not realize the full implications of its decision and that the closure of a major centre (the only one in Britain) of a new technology had been premature. At Earith too much faith was placed in an aspect of fundamental science which has quite rapidly become outdated. Professor Laithwaite himself, in a television interview last week, said that even since February, when support for THL was withdrawn, important discoveries have been made in the field of linear motor research. The vehicle under test at THL relied on air suspension but the Imperial College group has recently developed a motor which as well as providing propulsion also provides suspension and levitation. Such a motor, in principle, is far better than any previously developed, but whether it is a better prospect for large-scale development and, in the long run, a better commercial proposition can only be assessed after a model has been built and tested on an appropriate length of track. Here lies the nub of Professor Laithwaite's and the select committee's arguments. The government has arranged

for linear motor work and other aspects of the THL technology to be continued elsewhere but it is essential that the track be available for field tests of models.

Mr Heseltine was cool to the idea that the facilities at Earith be turned into a national centre when the select committee suggested this in July. It is hoped that he may even now admit that he was wrong and that such a centre should be given the wholehearted support of the government. Mr Airey Neave and the select committee seem to have no such faith in the minister, for they have turned directly to the Prime Minister in the hope that he will refer the matter to Lord Rothschild and the Central Policy Review Staff. There are few who would query Lord Rothschild's ability to make a judgment on the scale of support that linear motor research, work on high speed transport systems, and such related technology should receive in Britain. If the by now historic green paper on government research and development is anything to go by, Lord Rothschild would give a quick answer.

Britain in the past has suffered much from lost opportunities in the fields of novel means of transport. Remarks to the select committee by Mr John Peyton, Minister for Transport Industries, that the problems of the 1980s were impossible and those of the 1990s quite beyond him, although probably true, are deplorable. Planning for the future is one of the tasks of the Minister for Transport Industries and the future does not end when a political career might. Other countries, including the United States of America, have advanced at a faster pace than Britain in the past twenty years, in a large part because they have kept many more options open. At this stage of the development of linear motors and high speed suspension systems in Britain the options must be renewed, not rejected.

100 Years Ago



In the observations which I have to address to you I shall not attempt a general survey of a subject so vast and so varied as the manufactures of this country, nor shall I attempt to describe the many new and beautiful inventions and mechanical appliances which form a distinguishing feature of the age in which we live; but I shall endeavour to draw your attention to one of the new materials, namely *modern steel*—a material which, though of comparatively recent origin, has already become an important industry, and whose influence in the future seems destined to vie in importance with that resulting from the introduction of iron.

From the opening address to the British Association by the President of the Mechanical Science Section, W. H. Barlow, C.E., F.R.S.

From *Nature*, 8, 426, September 18, 1873.

OLD WORLD

Restrictions on Marine Research Come Closer

AFTER more than 100 hours of official meetings, countless corridor and coffee cup negotiations, and eight sweaty weeks in Geneva, the future of marine scientific research is still as much in danger as ever. The preparatory meeting for next year's Law of the Sea Conference (which is due to meet in Santiago in April if events in Chile in the last few days do not cause postponement) spent some part of its time in one of its sub-committees attempting to define scientific research and trying to decide how free it should be. At the end of the day a definition of research emerged, and several proposals were put forward as to how it should be conducted, but no guarantee that there will not be much tighter controls than currently exist emerged.

Scientific research is only one of many issues that faced the preparatory committee (the largest committee in the United Nations' history) during July and August. In essence next year's conference is intended to sort out the whole of the law of the sea, a brief that not only includes fishing and mineral and hydrocarbon rights in territorial waters, the so-called patrimonial waters, on the high seas and on the deep ocean floor, but also includes issues such as pollution, the establishment of an International Seabed Authority, defence—and scientific research.

The nub of the problem as far as science is concerned is that a block of the developing countries (notably the South Americans and some African states) are demanding that the proposed International Seabed Authority should regulate all scientific research on the high seas. Expeditions would have to be licensed by the authority, would have to carry an international observer and would have to submit their results to the authority before publication. This proposal is prompted by the fear that oceanography has largely economic, and possibly military, ends—a fear that is not much assuaged by the extent to which the United States Navy has in the past financed oceanography in the USA.

Hand in hand with these threatened restrictions on scientific research on the high seas comes the possibility of an extension of the restrictions on research closer to land. At present the only areas in which marine research is tightly limited is in territorial waters—the three or twelve mile strips just off shore. In these waters each country has complete sovereignty. Permission is needed for

research to take place, and while it is usually granted there are increasingly complaints from oceanographers about the difficulty of acquiring such permission quickly enough.

This regime is, however, likely to be extended. A number of developing nations took the stance early in the preparatory meetings for next year's conference (meetings that began five years ago) that patrimonial seas should be established that extend for 200 miles or to the outer edge of the continental shelf, whichever is the greater. In this area the country with the adjoining coastline would have rights over fishing and mineral and hydrocarbon resources, but would not have total sovereignty.

At present, under the 1958 Geneva convention, permission is already needed for research on the floor of the continental shelf, but research on the water column and its contents is unrestricted.

If the present proposals before the UN committee are approved, however, scientific research on the water column will also be subject to the adjoining coastal state's permission.

At first this proposal for a 200-mile patrimonial sea met with considerable opposition from the developed countries, but now it has received backing to a greater or lesser extent not only from the developing countries but also from Australia and Canada while even the UK has indicated some willingness to accept similar wide limits for resource rights. Attempts are still being made to protect scientific research, and the United States has tabled a proposal that those undertaking research should simply have to notify the relevant state a fixed number of days before the expedition arrives. This would mark a considerable relaxation of the current regime in territorial waters. But as one

EDUCATION

Mastering Doctorates

by our Correspondent

THE provision of 7,000 new postgraduate places in universities during the current quinquennium could be overgenerous unless the emphasis in research degrees is changed from PhDs to MScs, according to Professor B. A. Cross of the University of Bristol. At a symposium on the future of the postgraduate in the next decade, held at Leckhampton, the graduate college of Corpus Christi College, Cambridge, last week, Professor Cross, who is to become director of the Agricultural Research Council Institute of Animal Physiology at Babraham from April next, attacked the rapid growth of PhD student numbers, and accused the universities of "acquiescing to academic inflation". As a result the value of the PhD is being undermined and government money is being wasted, he said. Departments tend to acquire large numbers of PhD students as a status symbol, only to choose the PhD subject for the student and then to use him at least partly as a research assistant. Supervisors are also reluctant to give adverse reports on their students, even to the extent that they will help out with experiments and write the student's thesis.

PhD students, Professor Cross said, "use a lot of time, resources, energies and spiritual reserves of the academic staff who can usually be more creative

working with collaborators and post-doctoral fellows."

The answer to the problem, according to Professor Cross, is to develop a binary system of postgraduate education in which more students take MSc courses which allow the student to acquire new techniques and to make a disciplined attack on a problem. This suits better the needs of industry where often science is important but creativity is not. PhDs are needed much less by industry than by the universities.

Supervisors should not have to take on large numbers of PhD students, and need train a PhD student to replace them only once or twice in their thirty years' work. "We do not need a supervisor to produce six PhDs a year if we define the holder of a PhD as a creative scientist". As it is, 60% of current PhDs become invisible to science after graduating as they enter other careers, and the research councils and the Department of Education and Science could have saved a great deal of money by allowing these people to take MSc instead of PhD courses.

The key to the problem is to test a student's motivation while he is still an undergraduate. Research projects undertaken in first degree courses reveal those students with creative minds who have problems they want to solve, Professor Cross said. "I am very impressed with the abilities of undergraduates to make original discoveries; research should start at honours degree level".

delegate put it, the proposal seems to have a snowball's chance in hell at Santiago. The best that can be hoped for, it seems, is a regime in patrimonial seas no worse than that currently applying to research on the continental shelf under the 1958 Geneva Convention.

As for research on the high seas, the outcome really depends on who wins the battle to define the International Seabed Authority's role. Some developing countries are eager to establish a strong authority which would itself exploit the manganese nodules that cover certain areas of the Pacific. The world's nations would then be paid a percentage of the returns from the operation.

This proposal is being opposed largely by the developed countries (see *Nature*, **243**, 429; 1973; and **239**, 421; 1972). They argue that the cost of setting up such a body, the problems of running it internationally and the difficulty of staffing it with experts in what is a totally untried technology, make the proposal impractical, even if ideologically attractive. Their alternative is to have the seabed authority license areas of the ocean to interested states who would in turn hire the companies with the know-how actually to mine the nodules. Developing countries would benefit as much as developed, the argument runs, because they could also license the companies with the necessary expertise (all of whom, not unnaturally, are based in the developed countries). A third proposal emerged at Geneva which would do something to combine the two approaches, allowing the authority both to license areas of the ocean for exploitation and to organize the exploitation itself when it has the expertise.

What the final outcome will be remains to be seen. One theory is that the attacks on scientific research are being made in order to achieve one of the other objectives—the 200-mile patrimonial sea for example. But until the voting system has been worked out in New York later this year, and until nations are really putting their cards on the table, it is not possible to predict the end result with any certainty. It does, however, seem more than likely that scientific research in the waters above the continental shelf is likely to be hampered to a greater extent than at present.

DRUGS

'Paraquat' Attacked

PRESS reports that eleven-year-old Peter Holdsworth is the only person to have survived poisoning with the weedkiller 'Paraquat' are untrue. According to ICI, the makers of the weedkiller, it has recently been estimated that there have been twenty-two survivors from

sixty-four cases of severe poisoning. But Peter's recovery is surprising enough, and the treatment used at the Hammersmith Hospital is experimental enough, to have aroused considerable interest.

He was expected to die because he was excreting the poison at a rate of $5 \mu\text{g ml}^{-1}$ on the third day after swallowing it, which indicated a blood level of 'Paraquat' high enough to make lung damage inevitable. The usual course of 'Paraquat' poisoning is corrosive damage to the tissues of the mouth and gut, followed by kidney and liver damage—from all of which the patient can recover—but followed, after about two weeks, by fibrosis of the lungs from which there is no recovery.

Sufferers of 'Paraquat' poisoning usually die of suffocation because of lung damage, for which there is no known antidote. The question is, has the Hammersmith Hospital team now found one? The treatment involved three drugs. The least controversial of these was 'Beclamethasone', a corticosteroid which is already in use as a specific drug for the control of asthma. The Hammersmith team hoped that it would help to prevent the development of non-functional fibrous scar tissue in the lungs. But the effectiveness of such steroids administered to 'Paraquat' cases is still a matter of debate.

The administration of the other two drugs, neither of which is in general clinical use, was based entirely on theoretical speculation. 'Paraquat' seems to have a particular affinity for lung tissue, where it probably binds to cell membranes. A team at the surgical and toxicological units of the Edinburgh Royal Infirmary once transplanted a lung into a poisoned child only to see fibrosis set in because of the persistence of a residuum of 'Paraquat' in the thorax. The Hammersmith team was therefore looking for a chemical that might dislodge the 'Paraquat' molecule from its putative binding site on the membranes. They hit on 'D-propanolol' because it happens to bind to lung tissue and because it is at the moment under investigation at the Hammersmith Hospital for reasons totally unrelated to 'Paraquat' poisoning. It is, in fact, one constituent of the ICI heart drug 'Inderal', which is composed of a mixture of the D and L isomers of 'Propanolol'. The L isomer is the active constituent of 'Inderal', and the pharmacological action of the D isomer is still the subject of research. It was used in the treatment of Peter Holdsworth as a possible competitor for 'Paraquat' on the membranes of the lung tissue. Whether this was its actual effect, if indeed it had any, will be impossible to say without further research.

The rationale for 'Orgotein', the third of the drugs, seems to have been some-

what wilder. 'Orgotein' is the trade name for the enzyme superoxide dismutase, produced by Fisons. Superoxide dismutases are present in varying amounts in the tissues of the body, where they transform highly reactive (and therefore damaging) free-radical oxygens into molecular oxygen and hydrogen peroxide. It is known from research on plants that 'Paraquat' can be reduced by biological systems to free-radical oxygen which causes damage to plant cells—although it is still not clear how great a part free-radical damage plays in the destruction of weeds by 'Paraquat'.

The administration of 'Orgotein' to Peter Holdsworth was thus based on extrapolation from work on plants, with the aim of breaking down hypothetical free radicals which might contribute to the destruction of lung tissue. There is, however, no evidence for free-radical damage in 'Paraquat' poisoning in animals. Nor is there any evidence that free radicals are formed from 'Paraquat' in animal tissues. This would require a substantial reduction voltage which is available in plants in the photosynthetic reactions.

Furthermore, the reactions in question are intracellular and it is most unlikely that a macromolecule such as superoxide dismutase could penetrate the cell membrane. So all in all, the case for the therapeutic contribution of 'Orgotein' seems fairly dubious.

Until more data have been collected, and the clinical details of this particular case are published, it will of course be impossible to evaluate properly the last-ditch treatment which seems to have been so well rewarded at the Hammersmith Hospital. But the fact that a child has recovered in spite of having sustained some lung damage from a dose of 'Paraquat' will be enough to stimulate vigorous interest in the drugs used.

RESEARCH AWARDS

Anyone for an Award?

THE Science Research Council has had a 5% shortfall in applications for its research studentships. Some 200 studentships out of a total of 3,950 on offer are still vacant, and although not all departments and applicants have given their final answers on allocations it seems more than likely that there will be appreciably more studentships available than there are students to take them at the start of next term.

A slightly different story is found at the other research councils. At the Natural Environment Research Council all available awards will be granted, but the council's rejection rate for applicants for PhD awards has fallen from 15 to 20 per cent during the past few years, to virtually nil this year. But while applications for its 261 research student-

ships leading to a PhD are down, applications for MSc courses, for which the council provides about 170 grants, are up by about 20%.

The Science Research Council said this week that it is as yet too soon to be able to tell which subjects have been most affected, and the council could not even say whether applications for PhDs or for masters courses were hardest hit.

The Medical Research Council, which has just over 400 awards on offer, 320 for PhDs and just under 100 for masters' courses, has no such problems. A spokesman for the council said this week that applications were about the same as last year, although it looked as though a shortfall was likely earlier in the year. In fact over 1,000 applications were received.

What are the reasons for the fall in applications to SRC and NERC? Spokesmen for the councils are a little reluctant to speculate on the reasons for the reductions in applications except to point to the much improved job market for graduates this year, and to the publicity given over the past few years to the difficulty PhDs were experiencing in finding jobs. The attack on the PhD launched by the Confederation of British Industry when giving evidence to a House of Commons Select Committee recently is just one of the pointers.

It is also possible that graduates are following the trends that can be discerned in schools and first degree courses away from physics and chemistry and towards medical and social science. A further factor may be the size of the grant, while there have also been suggestions that more graduates with good firsts are entering industry rather than moving into research with the result that the quality of applicants for PhDs is lower than last year. The MRC says its figures do not support this, and NERC is adamant that the candidates that are filling its research studentships are "fully acceptable". Whether the situation will be the same among the SRC's depleted ranks will not become plain until the council finally completes its sums later this year.

HIGH ENERGY PHYSICS

Conventional CERN

THREE months after the decision was taken to incorporate conventional magnets, rather than superconducting magnets, in the super proton synchrotron now being built at CERN, progress is continuing apace. A spokesman for the organization said this week that although the civil engineers who are engaged in building the tunnel have run into some difficulties, for example they encountered a pocket of natural gas

which delayed progress earlier in the summer—there is at present no concern that a 400 GeV beam will not be available by late 1976.

There is little doubt that a ripple of disappointment ran through the high energy physics world with the announcement that no superconducting magnets will be incorporated in any phase of the design. But progress with superconducting accelerators around the world has been disappointing and the CERN council in June decided that the risks of non-conventional magnets would not be worthwhile. One of the problems with superconducting magnets of the size required for CERN is that there is no guarantee that every magnet manufactured will behave in exactly the same way.

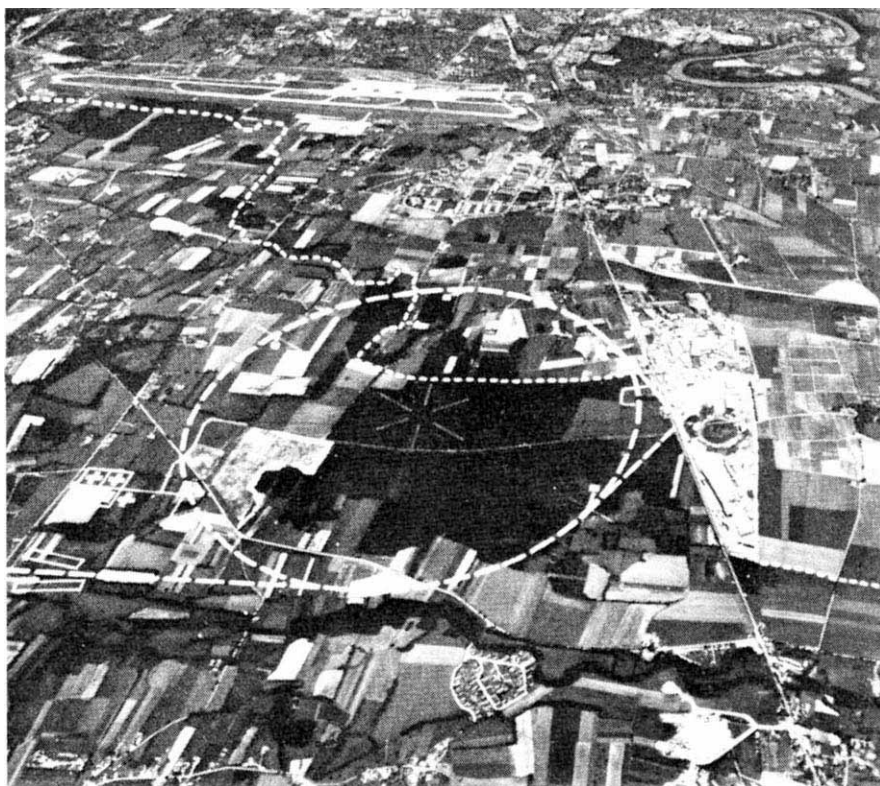
A further problem is that confidence with superconducting accelerators is at a low ebb following the failure of physicists at Stanford University to obtain a sufficiently large voltage gradient in their superconducting linear electron accelerator. The problems at Stanford are the same as those that were being attacked at least thirty months ago. Essentially they boil down to the quality of the surface inside the accelerator sections, which determines the voltage gradient which each section can withstand.

But the decision at CERN to forego superconducting magnets means that the remaining deadlines in the programme are more likely to be met than otherwise would have been the case. And, of course, conventional magnets

imply that the costs will be lower.

Two kilometres of the 6.9 kilometre accelerator ring have already been completed and the plans are for the tunnelling work to be completed by the spring of 1975, but the "mole" which is at present busily at work underground will have completed its work by the autumn of 1974. Installation of the magnets will, however, start in the completed sections of the tunnel in January 1974. All the components have now been ordered and some of the first magnets have already arrived on site. Two of the 32 Nord-10 computers which have been ordered for the accelerator have also been delivered.

Another decision taken in June means that the first beam out of the accelerator will be of 400 GeV and there will not be an intermediate stage where 200 GeV will be available. This is certainly an advance on a year ago when there was only a commitment to build a 200 GeV accelerator and the extra magnets to increase the energy to 300 GeV would only be included if "the physics interest makes the extra 100 GeV important". Now it seems that 400 GeV will be obtained without the project going outside its original budget. During 1973, the third year of the project, 188 million Swiss francs will be spent while it is estimated that the budget next year will be nearer SF200 million. It is a remarkable testimony to Dr J. B. Adams, the director general of the project, that costs in real terms have only increased by 6% a year during the past three years when all around there is high inflation.



Aerial view of CERN and the outline of the super proton synchrotron. The shorter dotted line is the Franco-Swiss frontier.

NEW WORLD

Elusive Pulse of US Science

by our Washington Correspondent

SCIENTISTS throughout the United States, who have been complaining bitterly in the past few years about budgetary cutbacks and unemployment, need little reminding of the fact that money for science is relatively more scarce now than it was in the mid-1960s. The figures speak for themselves. But how true are the dire predictions of a decline in science? And, in particular, has the financial squeeze seriously damaged the fabric and overall quality of science in the United States?

The National Science Board, the 25-member council which provides policy direction for the National Science Foundation, has been trying for the past year to develop the tools with which to take the pulse of the scientific effort in the United States, and to pinpoint warning signals which could indicate whether its health is in decline. The preliminary fruits of the endeavour, published last week*, provide a mine of information, and bring out some potentially alarming trends. But the board is the first to admit that there is little in its analysis so far that can be used to measure the overall quality and effectiveness of the scientific and technological effort.

The problem is, as Dr Herbert E. Carter, chairman of the National Science Board, points out in a covering letter to President Nixon, that the paucity of data has limited the report chiefly to dealing with resources—funds, manpower and equipment—and there are few measures of outputs from these resources. The budget makers in the Nixon administration, who like to run the country along the lines of a giant corporation are, however, more concerned with productivity and they are thus more likely to be influenced by figures that show that the output of US science has declined as a result of funding cutbacks since 1968.

Nevertheless, as far as resources are concerned, the board notes the following:

- Although total expenditures on science and technology show a steady increase from 1958 to 1972, when inflation is taken into account, there was a 6% decline between 1968 and 1971. Moreover, expressed as a proportion of the gross national product, total outlays on research and development dropped from 3.0% in 1964 to 2.5% in 1972.

- The most marked decline in spending after 1968 was in the federal govern-

ment's science budget which, if inflation is taken into account, shrunk by 12% between 1968 and 1972. The chief drop was in expenditures for space research, and the combined total for defence and space declined from 86% of the federal science budget in 1963 to a mere 73% in 1972.

- The numbers of active scientists and engineers in the US grew by about 50% between 1960 and 1971, reaching some 1.75 million. Unemployment, however, increased steadily after 1969, peaked at about 2.6 and 2.9% for scientists and engineers respectively in early 1971, and began to decline again in 1972.

The National Science Board also took a look at what has been happening in other countries, but found little coherent pattern. For example, spending on research and development expressed as a proportion of gross national product declined in France and the UK between 1963 and 1971, but increased in the USSR, Japan and West Germany. As for the number of scientists and engineers engaged in research and development per 10,000 population, the proportion declined in the United States after 1969, but continued to increase in the USSR, France and West Germany—by 1971, the number had reached 37 in the USSR, 25 in the United States and Japan, 15 in West Germany and 12 in France.

In an attempt to measure whether these various trends have affected the international standing of United States science, the board examined the volume of literature produced by United States scientists in eight scientific disciplines

(physics and geophysics, chemistry and metallurgy, systemic biology, molecular biology, mathematics, engineering, psychology, and economics). In seven of the eight disciplines, the board found that more literature is produced by scientists in the United States than in any other major developed country; the one exception was in chemistry and metallurgy, in which the USSR came top of the pile. Moreover, the survey also showed that in every field except for systematic biology and mathematics, United States publications receive more citations on average than those produced in other countries. For the two exceptions, UK scientists led the field, and in fact, they were also runners up to the United States in the other six areas of science.

The board intends to expand and refine the indicators in the next few years, and hopes that they will "assist in setting priorities for the (scientific) enterprise, in allocating resources for its functions and in guiding it towards needed change and new opportunities". Nevertheless, the board is quick to point out that "quantitative indicators, no matter how useful, are not a substitute for the experience and judgment of the scientific community". In view of that comment, it is perhaps worth noting that the report was put together in January, when the new arrangements for science policy had been announced, the President's Science Advisory Committee had been scrapped, and there was no provision for formal, independent scientific advice from the community to the makers of United States science policy.

RESEARCH SPENDING

More is Less

by our Washington Correspondent

THE latest set of figures on the federal government's spending on research and development, published last week by the National Science Foundation, confirm and extend the trends noted in the report of the National Science Board (see accompanying article). Based on estimates for the 1973 fiscal year and projected outlays in 1974, the figures show that when inflation is taken into account, the total science budget has remained static for the past 3 years. And, in spite of assurances to the contrary by Administration officials, there has been a marked shift in spending away from basic research towards applied research and development.

The figures show that basic research

received an increase of 2.7% in 1973 (a decrease of 1.0% if inflation is taken into account), and an absolute decrease of 2.0% is estimated for 1974, when the total is expected to be \$2,400 million. Development, on the other hand, is expected to get a 3% increase in 1974 and applied research an increase of about 5%.

The NSF's figures also show that the share of the total federal budget devoted to research and development dropped from 12.6% in 1965 to 7.2% in 1972, and has continued to decline to an expected 6.5% in 1974. Another trend which was noted by the National Science Board and which has been extended by the later NSF figures is that the greatest increases in spending have been devoted to the life sciences, which in 1973 and 1974 for the first time ever received more federal funds than engineering.

**Science Indicators 1972*. \$3.00. Available from the Government Printing Office, Washington DC 20402. Stock no. 3800-00146.

HEW

Budget Blues

ANOTHER senior official of the Office of Management and Budget (OMB) is expected to be appointed soon to a key position in the Department of Health, Education and Welfare, according to sources in the Administration. He is Mr Jack Young, at present Deputy Associate Director of OMB for Energy and Science, whose jurisdiction includes NASA, the Atomic Energy Commission, the National Science Foundation and the National Oceanic and Atmospheric Administration. Mr Young is in line for the post of Comptroller of HEW, a position which will put his hand on the Department's purse-strings and which will put him at the centre of the economy drive which is now taking place in the department.

A widely respected administrator, Young is expected to replace James B. Cardwell, the present Comptroller, whose nomination to the post of Commissioner for Social Security is awaiting Senate confirmation. The top two positions in HEW are already occupied by former OMB officials—Caspar Weinberger, Secretary of HEW, was Director of OMB and Under-secretary Frank Carlucci moved to the department from the post of Associate Director of OMB—and Young's appointment is sure to add fuel to the complaint that the department is being placed in the control of White House managers who have a brief to put a brake on its expenditures. Last week, for example, Mr Weinberger decreed a 75% cut in HEW public relations budgets and last month he announced that he has scrapped 119 of the department's 392 advisory committees. To say nothing of the fact that President Nixon twice vetoed HEW appropriations bills when Mr Weinberger was Director of OMB.

SAKHAROV

Academy Protests

by our Washington Correspondent

THE United States National Academy of Sciences has sent a sharp warning to authorities in the Soviet Union that further harassment of Andrei D. Sakharov could harm the growing scientific accord between the two countries. The warning came in a telegram and a longer message sent at the weekend by Dr Philip Handler,

NAS President, to Mstislav V. Keldysh, President of the Academy of Sciences of the USSR. The telegram said, in part, that 'harassment or detention of Sakharov will have severe effects upon the relationships between scientific communities of the United States and the USSR and could vitiate our recent efforts towards increasing scientific interchange and cooperation'.

Sakharov, who has been in trouble with Soviet authorities for his criticisms of Soviet society which have appeared in the western press, was elected a foreign member of the United States National Academy of Sciences in April this year. He has been officially warned by the Deputy General Procurator about his activities and at the end of August a letter signed by 40 members of the USSR Academy of Sciences, attacking his views, was published in *Pravda* (see *Nature*, 245, 2, 1973).

The NAS protest says that "It was with consternation and a sense of shame that we learned of the expression of censure of Sakharov's contributions to the cause of continuing human progress that was signed by 40 members of your academy". The message says that the attack "revives memories of the failure of our own scientific community to protect the late J. R. Oppenheimer from political attack. The case of Andrei Sakharov, however, is far more painful for the fact that some of our Soviet colleagues and fellow scientists are among the principal attackers when one of the scientific community courageously defends the application of the scientific ethos to human affairs".

In the past year or so, a number of scientific agreements have been signed between the governments of the United States and the Soviet Union, and the level of interchange between Soviet and American scientists is perhaps greater now than ever before. The NAS message warns, however, that "were Sakharov to be deprived of his opportunity to serve the Soviet people and humanity, it would be extremely difficult to imagine successful fulfilment of American pledges of binational scientific cooperation, the implementation of which is entirely dependent on the voluntary effort and goodwill of our individual scientists and scientific institutions".

The academy's protest was drawn up by the executive committee and telephoned to those members of the NAS council who could be reached. None opposed it. It was not, however, cleared with the State Department or the White House, and stands in marked contrast to the official United States Government position of "no comment". Dr Henry Kissinger, the Secretary Designate of State, said last week during hearings on his confirmation, that although he is "certainly dismayed by the

conditions that Academician Sakharov reports", the United States Government should not meddle in the domestic affairs of the Soviet Union.

Asked for his views on the protest this week Dr H. Guyford Stever, Director of the National Science Foundation and Chairman of the Joint Commission which oversees the implementation of the joint US-USSR scientific agreements, said that he is sure that the joint programmes will go ahead because of their importance to world peace.

ENERGY

Misplaced Attack

IT is a familiar tactic in American politics for the President to rebuke Congress for dragging its feet on legislation proposed by the Administration. But last week, President Nixon added a fresh twist to the ritual—he accused Congress of failing to act on an Administration proposal which has not even been submitted. Congress, he said during his press conference, has not yet acted on seven major proposals for dealing with the energy crisis, "including, for example, research and development in the field of coal and other areas". The fact is, however, that although President Nixon announced in June, as part of his latest pronouncement on energy policy, that he would seek an extra \$100 million this year for energy research and development—about half of it for coal research—no such proposal has been sent to Capitol Hill.

The situation was even further confused earlier this week, when President Nixon sent a State of the Union message to Congress outlining the Bills on which he wants swift action. Acknowledging that he had recently announced plans for a federal programme of research on new energy sources, costing \$10,000 million over the next five years, President Nixon said "No legislative action is needed by the Congress this year to provide funding, but it will be necessary for the Congress to approve such funding in the years ahead". The original plan, however, was to start the five-year programme in the 1975 fiscal year, but to add an extra \$100 million to this year's budget to get things started. Asked to clarify the situation, an official of the Office of Management and Budget could offer no explanation, but confirmed that no supplemental appropriations bill was being drawn up. Somewhere, however, \$100 million has been lost.

NEWS AND VIEWS

Earthquakes and the Chandler Wobble

THE matter of a neutron star can theoretically be a solid, or a solid mantle enclosing a liquid core, and thus somewhat similar to the Earth. This highly theoretical solid necessarily invokes the attention of highly theoretical solid state physicists and so it comes about that a new variety of scientist pays attention to some old problems about rotating elastic bodies, earlier considered in relation to the Earth. Furthermore, if the neutron star is analogous in structure to the Earth, it may exhibit phenomena analogous to earthquakes, a possible interpretation of sudden changes in the frequency of pulsars. Hence these scientists also approach these problems with seismicity in mind. Now, Pines and Shaham return from consideration of neutron stars to take a new look at these matters in relation to the Earth itself (see page 77 of this issue of *Nature* and *Nature Physical Science*, **243**, 122; 1973).

Pines and Shaham in their analysis define tensors, having the form of moment of inertia tensors, which represent (as far as quadrupolar terms) the departure from spherical symmetry in the Earth's moment(s) of inertia δI , its configuration δI_c , its distribution of density δI_d , and (this being where the novelty of their treatment enters) that part of the Earth's asphericity which is sustained by shear stresses in the solid, defined as $\delta I_s - \delta I_c$. They find it possible to estimate all of these from the available observational data. Their analysis leads to the conclusion that the Earth holds an elastic energy store of about 10^{25} J, mostly due to insufficient oblateness for elastic equilibrium but to some extent (10%) due to a non-optimal direction of the pole of flattening. This "angular" part of the elastic energy is much larger than has appeared in any previous estimates, which has important consequences for the effect of superposed tidal stresses.

Pines and Shaham adopt the very acceptable hypothesis that earthquakes occur to reduce the elastically stored energy in the Earth, and plausibly assume non-linear mechanical properties such that an earthquake will be triggered when the elastic energy exceeds a sufficient magnitude for a sufficient time—so that longer period variations in elastic energy are emphasized by comparison with the larger variations of short period, such as diurnal tides. One such variation with a period of 6 or 7 yr arises from interference between the annual term and the Chandler wobble period in the polar tides.

Euler, in 1765, calculated that the Earth should have a free nutation period of 10 months. Observations failed to reveal such a motion, but in 1891 S. C. Chandler, a merchant of Cambridge, Massachusetts, analysed discrepancies in determinations of latitude and discovered a small wobble of the Earth with a period of 14 months and an amplitude of polar displacement of about 6 m; then in 1892 Lord Kelvin was able to tell the British Association that Euler's calculation had been wrongly made for a rigid Earth, and Newcomb had been able to show that elastic yield in the Earth would account for the lengthening of period.

The persisting problem has been to discover what source of energy maintains the Chandler wobble, which should be damped out by tidal friction. Earthquakes have been

suggested as a driving source, but are inadequate to account for the observed amplitude of wobble if they occur randomly in time. Pines and Shaham's theory, however, suggests preferential triggering of earthquakes at intervals of 6 or 7 yr, in a consistent phase relationship to the Chandler wobble that is right for the maintenance rather than the suppression of the wobble. Whitten, in 1970, examining the variations in annual seismic energy release from 1900 onwards, found evidence of a 7 yr periodicity and suggested a connexion between this periodicity and polar motion. Earthquakes occurring with correct preferential phasal relationship to the Chandler wobble as predicted by Pines and Shaham's theory can keep it going.

To attach importance to this theory, one is not obliged to accept the authors' "scenario" according to which the present 10^{25} J of elastically stored energy is the residue of a much larger quantity created in an "elastic energy epoch" some 10^8 or 10^9 yr ago. The seismic energy release rate of 10^{18} J yr⁻¹ is much exceeded by the heat flow from the Earth, 50 mW m⁻² making 6×10^{20} J yr⁻¹, and it is no less compatible with their theory that the unshapeliness of the Earth, and its consequent elastic energy store, is continuously maintained by thermally induced transport of matter associated with this heat flow. F. C. F.

Jupiter's Magnetosphere

WITH two spacecraft on their way to Jupiter, considerable theoretical effort is being made to predict details of the planet's environment. In December of this year when Pioneer 10 reaches its point of closest approach, 2.86 R_J (Jupiter radii), many of these predictions can be tested.

One aspect of Jupiter's environment which has received particular attention is its magnetosphere and the associated trapped radiation belts. Recently, Mead of NASA Goddard Space Flight Center and Hess of the Environmental Research Laboratories, Boulder, Colorado, have shown that Jupiter's satellites may appreciably modify the particle fluxes trapped in the Jovian radiation belts (*J. geophys. Res.*, **78**, 2793; 1973). Five (Amalthea, Io, Europa, Ganymede, Callisto) of Jupiter's twelve satellites lie entirely within the magnetosphere.

The fact that Jupiter has a magnetosphere was deduced from the study of radio emissions from the planet. The 10.4 cm radiation was first discovered by Sloanaker (*Astr. J.*, **64**, 346; 1959) and later shown not to come from the surface of the planet but to have a brightness distribution which peaks in the equatorial plane at an altitude of 0.9 R_J . The radiation also has a strong linearly polarized component which suggests that it is synchrotron radiation from high energy electrons trapped in a magnetic field. Decametric radio bursts are also observed from Jupiter with frequencies ranging from 38 MHz down to the lowest frequency which can penetrate the Earth's ionosphere. On the assumption that this radiation is at the electron gyrofrequency close to the planet one can conclude that the surface magnetic field

strength of Jupiter must be about 10 gauss (compared with 0.3 gauss at the equator for the Earth's field). Because of its greater magnetic field and because of its distance (5.2 a.u.) from the Sun, the front or bow of the Jovian magnetosphere is expected to lie at about $50 R_J$ from the planet compared with $10 R_E$ (Earth radii) for the Earth. Unlike the Earth where the Moon lies outside the magnetosphere, except when it passes through the distant tail region, the Jovian magnetosphere encloses the five innermost satellites.

Mead and Hess studied the ability of these satellites to sweep up energetic protons and electrons as they diffused in through the magnetosphere from the solar wind. They concluded that the sweeping up process is so efficient that the inward diffusing particles should be reduced by several orders of magnitudes at Europa ($9.5 R_J$) and none should diffuse past Io ($5.9 R_J$) and Amalthea ($2.5 R_J$). The times calculated for electrons and protons to diffuse past a given satellite range from 137 years at Amalthea to 0.002 days at Callisto ($26.6 R_J$). These times are long compared with the absorption (by a satellite) lifetime in the case of Amalthea, Io and Europa, approximately equal for Ganymede and short for Callisto. Thus it is the inner three satellites which should primarily limit inward diffusion and prevent the extension of the trapped particle region closer to the planet than about $6 R_J$ at the equator.

The question that these results raise is how the trapped electrons can get close enough to the planet to produce the synchrotron radiation which is known to come from altitudes of less than one Jupiter radius. Mead and Hess offer two possible solutions to the problem: either Jupiter's inner satellites do not sweep up particles as efficiently as the simple theory would suggest or there are other processes, unknown at the Earth, which lead to the rapid inward diffusion of protons and electrons. The authors point out that if, for example, the inner satellites had an inherent magnetic field then this would deflect electrons and reduce the sweeping up effect. Protons, however, because of their greater momentum would still probably be absorbed by the satellites. This would not necessarily be inconsistent with the observations because there is no direct evidence of protons trapped close to Jupiter, the radio emissions

being produced entirely by electrons.

The second suggestion can certainly be tested by Pioneer 10 which will pass close enough to the planet to determine whether significant fluxes of protons exist, in the equatorial plane, inside the orbit of Io.

From a Correspondent

GENE CONTROL

Chasing the Messengers

from our Molecular Genetics Correspondent

ONE of the most critical parameters of gene expression in eukaryotic cells—and one of the least well defined—is the stability of messenger RNA. In bacteria, it is the very short half life of messenger RNA—measured in minutes—which permits the control of initiation of transcription to act as the critical step in the expression of an operon. In eukaryotic cells, messenger RNA has been known for some time to be much more stable, but accurate measurements of its lifetime have been made only recently. In two recent articles, Singer and Penman show that the population of messengers in HeLa cells may fall into two classes of stability.

Estimates for the half life of messenger RNA in several types of cell were made some years ago by following the decay in protein synthesis after transcription of messenger RNA was blocked by the addition of actinomycin. These estimates were generally of the order of 2 or 3 h. By assaying the decline in messenger RNA itself directly, Singer and Penman (*Nature*, **240**, 100; 1972) first showed that the assumptions upon which these estimates rested are not valid.

If the decline in protein synthesis after addition of actinomycin is due to degradation of previously existing messengers, the total number of polysomes in the cell should also decline. And when measured directly, the amount of messenger RNA should of course also decrease. But the polysomes extracted from HeLa cells treated with actinomycin sediment more slowly than those of untreated control cells and for several hours after the treatment do not show the expected decline in amount. This seems to be due to a slower rate of initiation of protein synthesis in the presence of actinomycin, a conclusion which implies that previous measurements of the decline in protein synthesis may have followed the decrease in initiation rather than in messenger content.

Direct assay of messenger content has become possible recently with the discovery that mRNA contains a sequence of polyadenylic acid (poly (A)); several methods are available for the bulk isolation of RNA molecules containing

poly (A) and by using one such method Singer and Penman showed that in the first 5 h after addition of actinomycin to HeLa cells there is little decline in the content of messengers containing poly (A). This argues that the half life is appreciably longer than previous estimates.

In more detailed measurements, Singer and Penman (*J. molec. Biol.*, **78**, 321; 1973) now report that two methods for measuring the lifetime of messenger RNA in HeLa cells show that its degradation does not follow a simple exponential decline. One method is to measure the decay in the presence of a radioactive label in the poly (A)-containing fraction after a brief period of pulse labelling; an alternative is to compare the continuous labelling of mRNA to rRNA both at the beginning of a labelling period and also later when a steady state has been reached in the presence of label.

When cells were labelled briefly with uridine and the label in mRNA followed over some days, the pattern of decline showed no one half life but can be fitted by assuming two populations of mRNA, one declining with a half life of 6–7 h and the other suffering degradation with a half life of about 24 h. By labelling messenger RNA with ^{14}C -uridine first and then with ^3H -uridine some 19 h later, it was possible to show that about 60% of the mRNA decays rapidly and about 40% decays more slowly. Measurements made in steady state conditions showed that the amount of messenger RNA is about 5.2% of the amount of ribosomal RNA in the cell. Of this mRNA, about 33% comprises the rapidly decaying species and about 67% possesses a longer lifetime.

Further confirmation that experiments in the presence of actinomycin do not provide a reliable assay of messenger stability was obtained by measuring the lifetime of messenger in the presence of actinomycin. The cell still contains two populations of mRNA in these conditions, but the more rapidly decaying then displays a half life of about 4.5 h whereas the longer lived has a half life of about 12 h. Messenger RNA may therefore decay more rapidly in the presence of actinomycin.

The most important implication of these results for models of gene control in eukaryotic cells is that more than one mechanism may exist to degrade messenger RNA. Because there are two populations of messenger molecules, each must be recognized by a different decay system or each must have a different susceptibility to a common degradation system. Viewed in the perspective of the mechanisms which may be responsible for maturing messenger RNA from its giant precursors, these experiments point towards the conclusion that each stage of the life of messenger RNA may

be under specific control, a situation distinct from that of bacteria where all messengers seem to suffer degradation almost immediately after their transcription (presumably by non-specific systems). One possible implication is that translational as well as transcriptional control may be important in mammalian cells.

INSECT REPRODUCTION

Fertilization in Housefly

from our Insect Physiology Correspondent

THE spermatozoa of insects, whether introduced into the female by means of a spermatophore or by direct insemination, must first gain access to the receptaculum seminis or spermatheca for storage, and subsequently to the vagina where fertilization of the eggs takes place. The extent to which these movements are brought about by mechanical forces exerted by the ducts of the female, or by the active migration of the spermatozoa themselves, is still obscure and may well vary in different species.

The best known example of mechanical control is in the queen bee, where a muscular pump regulates the transfer of spermatozoa from the spermatheca to the vagina. But active movements of the spermatozoa, induced by various glandular secretions, are usually believed to be the means of transfer. When the spermatozoa reach the egg as it enters the vagina at ovulation, they must surely migrate actively to find the micropyle, and must then be able to penetrate the covering membrane of the oocyte.

Leopold and Degrugillier (*Science*, **181**, 555; 1973) now show that the accessory glands in the female housefly (*Musca domestica*) are not needed to bring about the active migration of the

spermatozoa to the spermatheca, which is unaffected by extirpation of these glands. That is in agreement with the conclusion of Davey, a good many years ago, that the opaque secretion from certain of the accessory glands of the male in *Rhodnius* induces peristaltic movements in the genital ducts of the female, which serve to transport the sperm to the receptaculum. On the other hand, Leopold and Degrugillier show that removal of the accessory glands in the female housefly leads to a reduction in fertility to less than 1% of that in normal flies.

The egg enters the "anterior chamber" just behind the point of junction of the common oviduct and the vagina. Here it is held for several seconds only while from one to four spermatozoa enter the micropyle and make their way into the ooplasm. In the absence of female accessory glands the sperm remain aggregated near the entrance of the micropyle. Whether this striking effect of the accessory gland secretion on fertility is due to activation of sperm movement, or whether it induces some change in the vitelline membrane which increases its permeability for spermatozoa, remains undetermined.

HORMONES

Sites of Action

from a Correspondent

It takes a brave man to attempt to turn the tide of evidence that oligopeptide hormones act by activation of nucleotide cyclases. Sharma (*J. biol. Chem.*, **248**, 5473; 1973) now reports, however, that adrenocorticotrophic hormone (ACTH), when added to isolated adrenal cells, affects the conversion of (20S)-20-hydroxycholesterol to pregnenolone; this effect is insensitive to cycloheximide

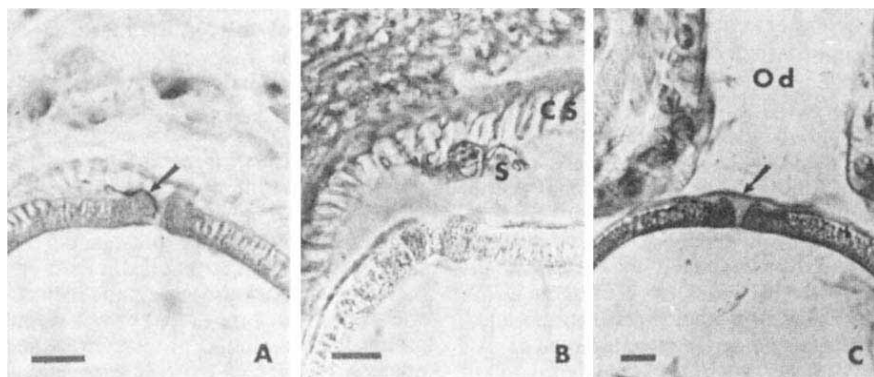
and is not mimicked by cyclic AMP or its derivatives. Previous observations that the complete conversion of cholesterol to pregnenolone is modulated by cyclic AMP are not contradicted, however, as the first step in the conversion, the formation of (20S)-20-hydroxycholesterol from cholesterol, is found to be sensitive to both cycloheximide and cyclic AMP.

The significance of Sharma's observation presumably depends on the relative rates and sensitivities to ACTH stimulation of the two reactions. It has been reported previously that there are two different classes of binding site for ACTH; and two different receptors may be responsible for the two actions of the hormone. Sharma's experiments will probably be repeated elsewhere, as the unifying hypothesis of cyclic AMP activation is unlikely to be easily discarded.

Two classes of renal binding sites have been reported for calcitonin (Marx *et al.*, *ibid.*, 4797). These authors very carefully document the activity of their ¹²⁵I-calcitonin by investigating its chemical purity and ability to activate adenylate cyclase, thereby forestalling the common criticism of this kind of study—the poor characterization of a labelled hormone. The degradation of the peptide, another difficulty in such studies, was reduced by the addition of ACTH, which reduced degradation but did not block binding. The sites with high affinity and low capacity for the hormone are thought to be where the biological potency resides, and are clearly distinguishable from the sites of hormone degradation. Although two classes of binding sites have been reported for several systems, it is not clear in every case that one class can be identified with the receptor-cyclase, and the other with degradation. Considerably more study will be required to determine whether this is an observation of physiological relevance.

Any enzymologist, asked to interpret the probable mechanism of hormone-stimulated adenylate cyclases, would surely automatically invoke "conformational change". Physical measurements in poorly purified membrane preparations are obviously not feasible, and the use of chemical modification reactions is a sensible approach. Storm and Dolginow (*ibid.*, 5208) have utilized the known reactivity of adenylate cyclase with sulphydryl reagents and found that glucagon increases about ten times the rate of inhibition of adenylate cyclase activity by iodoacetamide. Such an enhancement, besides being an excellent indication in itself of conformational change, may prove useful in chemical studies of more purified preparations.

Klein *et al.* (*ibid.*, 5552) present evidence which they interpret as the dis-



Sagittal sections of the micropyle region of eggs within reproductive tracts of female houseflies taken in the process of oviposition. (A) Sperm (arrow) are penetrating the micropyle of an egg held within the anterior chamber of a sham-operated female. (B) Numerous sperm (S) have coalesced into a single mass in the anterior chamber of a female without sex glands. Flexible cuticular spines (CS) project into the lumen of the anterior chamber (phase contrast illumination). (C) Arrow indicates the presence of the micropyle cap on an egg that has stopped within the common oviduct (Od) of an ovipositing female. Scale bars, 10 μ m. (Reproduced, by permission, from Leopold and Degrugillier, *Science*, **181**, 556; 1973.)

sociation of the glucagon binding site in a "solubilized" adenylate cyclase of myocardial origin. Glucagon binding could apparently be separated from adenylate cyclase activity by prior incubation with the hormone. The adenylate cyclase in the detergent used has been previously reported to be glucagon insensitive, however, so the authors are to be commended for their restraint in referring only to a glucagon binding site, and not to a receptor. The use of SDS-acrylamide gels to determine the molecular weight of the complex, using the ^{125}I -glucagon as a marker, depends on the incomplete denaturation of the binding component, and the resulting value should perhaps be regarded with caution.

Because of the difficulties of solubilizing hormone-sensitive adenylate cyclases, and the general lack of sensitivity following the removal of lipids, there has been considerable speculation about an obligatory role for lipids in the macromolecular complex. Kreiner *et al.* (*Proc. natn. Acad. Sci., U.S.A.*, **79**, 1785; 1973) have detected a phenomenon which may be dependent on the lipid components—a temperature dependence of the energy of activation of the glucagon-stimulated hepatic adenylate cyclase. The effect is not seen in the fluoride or prostaglandin E_1 stimulation. As the authors note, although the mole fraction of cholesterol is high (about 0.3), indicating a small bulk phase transition which may be at a temperature rather different from that observed, it is quite possible that the observed transition is restricted to the environs of the enzyme, where the lipid composition could be markedly different from the bulk. A proper demonstration of protein or lipid as the temperature-sensitive component must presumably await the development of better techniques for reconstitution studies.

PSYCHIATRY

Biochemical Psychoses

from a Correspondent

MOST people with untreated phenylketonuria (PKU) are mentally retarded and unlikely to have children, but some for unknown reasons are of normal intelligence. It now seems, however, that women with undiagnosed PKU yet of normal intelligence are in danger of producing mentally retarded children. The reason for this seems to be that the high blood levels of phenylalanine in these women can damage the foetus (Perry *et al.*, *New Engl. J. Med.*, **289**, 395; 1973).

Phenylketonuria is a hereditary disease which occurs in one in 20,000 births and is caused by lack of the enzyme phenylalanine hydroxylase which converts phenylalanine to tyro-

sine. In Britain all infants are screened for PKU in the first few weeks of life either by a blood test—which is more reliable—or by a urine test based on detection of the excess phenylpyruvic acid produced as a result of the excess phenylalanine. Untreated, PKU leads to mental retardation, behavioural disorders with psychotic features and fits.

This new work, carried out in British Columbia, arose from an investigation of a patient who had been previously unsuccessfully treated with electroconvulsive therapy (ECT) and drugs for psychotic episodes but was finally referred for biochemical investigation at the age of 46, possibly as a result of the low IQs—25, 62, 79 and 59—of her four children. She was found to excrete large amounts of phenylpyruvic acid, have a very high blood level of phenylalanine and therefore had PKU. Her IQ was 83.

Two of her three sisters, who were of normal intelligence, also had high phenylalanine levels, and all their children were slow learners at school, although their IQs were not recorded. The third sister had normal levels and children with good school records. The only brother, unmarried, again had high phenylalanine levels, although he was a university graduate. The patient's parents were found to be heterozygote for PKU, as were her children and her siblings.

The authors have reviewed all well-documented similar cases occurring in 1972, and find that they support the

picture of high maternal phenylalanine levels being associated with mental retardation in their children. The higher the phenylalanine levels the more severe the retardation is likely to be.

Ideally, of course, all cases of PKU should be identified by screening in the first or second week of life, but this work shows that possibly this should be repeated on all pregnant women. Further work may show that reducing the phenylalanine levels in the blood by a suitable diet may prevent damage to the foetus. Another moral to this tale is that all patients admitted to mental hospitals ought to undergo biochemical investigation in case there is a recognizable basis for their mental disturbance, otherwise patients may in some cases receive inappropriate treatment.

SLIME MOULDS

mRNA Metabolism

from a Correspondent

THE cellular slime mould *Dictyostelium discoideum* has long been championed as an ideal model system for the study of morphogenesis and differentiation in metazoan organisms. Two papers by Firtel and colleagues in the latest issue of the *Journal of Molecular Biology* (**79**, 295 and 315; 1973) suggest, however, that, apart from assisting in these more exalted aims, the slime mould also has a good deal to offer in the way of information about a more basic cellular activity, namely, the synthesis and pro-

13S DNA in *E. coli* Ribosome Preparations

IN citing DNA as a component of *Escherichia coli* ribosomal preparations Stygal and Hindley (in *Nature New Biology* next Wednesday, September 19) are anxious to prove that this is not due to contamination by viruses or fragments of the bacterial genome.

The authors discount the possibility that the DNA is viral in origin by treating the DNA-ribosome complex with DNase before phenol extraction. The DNA is degraded and they reason that, had it been part of a virus, its protein coat would have protected it from degradation.

More evidence is presented that the DNA does not originate from the bacterial genome. First, the monodisperse 13S DNA is shown to be bound to a component in the ribosome preparation and not merely to cosediment with it. Second, when the ribosomes are prepared so as to minimize shearing of DNA (and maintain its high molecular weight), the low molecular weight DNA-ribosome complex can still be isolated. Third, although the base composition of the DNA shows it to be double stranded, the G plus C content is 58.2%

compared with 50% for total *E. coli* DNA.

Dissociation occurs when the DNA-containing complex is brought from 10 mM to 0.1 mM Mg^{2+} . This makes it unlikely to be a bacterial relaxation complex which is stable in the absence of Mg^{2+} . DNA-RNA polymerase and DNA-RNA-RNA polymerase complexes, which might otherwise have been considered as the *in vivo* site of the 13S DNA, are similarly excluded.

Dissociation also occurs when the complex is treated with T_1 RNase. This leads Stygal and Hindley to suggest that the complex might represent mRNAs in the process of transcription with 30S subunits already associated. It would be thought, however, that after attachment of the 30S subunit, the 50S subunit would combine to form the initiation complex, but although DNA is found in ribosomal preparations it is not found in the 70S fraction. The authors' apparent difficulty in suggesting any explanation for this unexpected observation may be due to uncertainty as to the exact binding site of the DNA in their ribosomal preparations.

cessing of messenger RNA. This information has come from the application of a few simple techniques, in particular that of identifying RNA molecules containing poly (A) sequences by their binding to poly (U) sepharose.

About 90% of the cytoplasmic poly (A)-containing RNA, which has a sedimentation coefficient of 8–30S, is found in polysomes and is therefore almost certainly messenger RNA. Each mRNA molecule has a stretch of 100–200 adenylic acid residues at the 3' end, and about 90% of each molecule hybridizes to unique sequences in the DNA, leaving only 10% to anneal to repetitive DNA. Poly (A)-containing RNA molecules in the nucleus, on the other hand, are larger than those in the cytoplasm, though only by about 20%, and a greater proportion of each molecule hybridizes to reiterated DNA. The nuclear RNA sequences hybridizing to repetitive DNA are at the 5' end of the molecule and are about 300 nucleotides long.

From these and other observations using pulse-chase techniques, Firtel and Lodish propose the following model for mRNA metabolism in the slime mould: RNA is transcribed from DNA, beginning at a repeated sequence, running through a unique sequence and ending in a second short repeated sequence. Poly (A) is then added post-transcriptionally and most of the 300 nucleotides at the 5' end are removed before the molecule enters the cytoplasm, where it rapidly attaches to polysomes. This model has obvious implications for the arrangement of repetitive and single copy sequences in the DNA, and must certainly be elaborated upon in higher organisms where much larger mRNA precursors are present and more of the heterogeneous nuclear RNA never reaches the cytoplasm.

In the course of this work Firtel, Baxter and Lodish made some important observations which have subsequently upset long-held ideas about the regulation of gene expression during the development of *Dictyostelium*. After the vegetative amoebae have aggregated to form the motile pseudoplasmodium there is a sequential increase in the activity of a number of enzymes, such as those concerned with the synthesis of the "slime" sheath. Earlier studies, in which actinomycin D was used to inhibit total RNA synthesis by about 90%, had suggested that the messenger RNA for certain of these enzymes—for example, UDP-glucose pyrophosphorylase—is synthesized several hours before it is translated and until then is stored in a "masked" or inactive state. Firtel *et al.*, using their technique of selecting poly (A)-containing RNA molecules, show that very high doses of actinomycin D do not in fact completely inhibit the synthesis of mRNA and that this can

only be achieved with high doses of actinomycin D and daunomycin (another DNA intercalating drug) together. Their results using these two drugs suggest that mRNA is translated soon after it is synthesized and that there is no intervening translational control mechanism.

The reason for *Dictyostelium*'s resistance to actinomycin D is not clear; the unique sequence DNA has a very low G+C content compared with other eukaryotes and the "slime" sheath may restrict entry of the drug. These findings, however, will undoubtedly serve as a cautionary tale against overinterpretation of other results using actinomycin D in developing systems.

EARTH'S MAGNETIC FIELD

Pacific Window in Doubt

from our Geomagnetism Correspondent

ALTHOUGH the Earth's magnetic field is largely dipolar, it also possesses non-dipole components which fluctuate much more rapidly with time. Almost all of the secular variation which has been observed during the past few hundred years may be attributed to changes in the non-dipole part of the field having periods in the range 10^2 – 10^3 yr, but over longer time scales there is an additional component in the secular variation due to wobble of the dipole with a periodicity of 10^4 – 10^5 yr. Of course, because the geomagnetic field has only been observed in detail for about 150 yr, the full ranges of non-dipole changes and dipole wobble have not been measured

directly. But both types of variation contribute to the scatter of palaeomagnetic directions and, conversely, such scatter may be analysed to give estimates of secular variation in the past (palaeosecular variation).

Numerous analyses of this type have been made using rocks from various parts of the world; but perhaps the most important are those which purport to show that for at least several million years the secular variation (and thus, by implication, the non-dipole field) in the central Pacific region has been anomalously low. Certainly the non-dipole field there is demonstrably low at present; and studies of lava sequences in Hawaii (see, for example, Doell and Cox, *J. geophys. Res.*, **74**, 4857; 1969) suggest that the state of affairs is far from temporary. Why this should be so is far from clear; but one interpretation is that there is some inhomogeneity in the lower mantle beneath the central Pacific which either shields the region above from the field variations seen elsewhere or reacts in some way with the fluid core to suppress the corresponding part of the non-dipole field altogether. In short, the low figure for the central Pacific field, if real, has important geophysical implications.

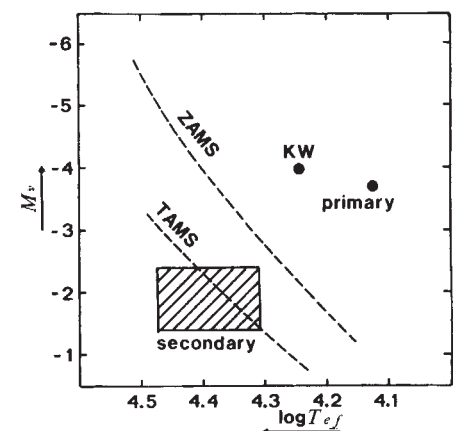
But is it real? Up to now the existence of the so-called Pacific window has been widely accepted even though its physical cause is uncertain. Aziz-Ur-Rahman and McDougall (*Geophys. J.*, **33**, 141; 1973) now suggest, however, that the phenomenon may be more apparent than real because of the pos-

Nature of Beta Lyrae

If nothing else, the suggestion that black holes have been discovered in binary systems has certainly stirred the theorists into proposing alternative models. The latest contribution to the discussion comes from Kříž, who presents in next Monday's *Nature Physical Science* (September 17) a persuasive argument that β Lyr does not contain a black hole, but rather represents an example of Case B mass exchange in a close binary.

Although the secondary is certainly underluminous, Kříž argues that this underluminosity was exaggerated by previous workers. From OAO observations and other data, he concludes that the secondary is of type B0–B2, which corresponds to a main sequence star with the mass estimated for the secondary of β Lyr. Combining the evidence in a Hertzsprung–Russell diagram (see figure), Kříž's estimates of the properties of the secondary fall plausibly about the terminal age main sequence (TAMS) which Stothers has determined for the stage at the end of core burning when core temperature reaches a minimum (*Astrophys. J.*, **175**, 431; 1972).

The real problem, says Kříž, is not "why is the secondary underluminous?" but rather "why is the primary overluminous?". Even so, one model of Case B mass exchange in a $9 M_{\odot} + 3.1 M_{\odot}$ binary leads to a primary comparably overluminous (KW in the figure),



falling rather above Stothers's zero age main sequence (ZAMS). The black hole hypothesis cannot explain this overluminosity, and that seems to be powerful evidence against it.

sible use of insufficient data in previous studies. Their own data come not from the central Pacific but from Norfolk and Philip Islands to the north of New Zealand in the south-west Pacific, where the present non-dipole field is high (of the order of 9,000 γ). Nevertheless, the results share certain features with the Hawaiian results—and Aziz-Ur-Rahman and McDougall's point is that their explanation for these features in the case of the Norfolk-Philip data may also be applicable to the Hawaiian data.

Norfolk and Philip Islands comprise basaltic lavas and tuffs erupted between 3.1 and 2.35×10^6 yr ago, although within this period eruption alternated with intervals of quiescence. The rock samples studied by Aziz-Ur-Rahman and McDougall covered all periods of eruption which, in magnetic terms, included the early Matuyama reversed epoch, the Gauss normal epoch and the Mammoth reversed event within the Gauss. The critical fact to emerge from the palaeomagnetic study of more than 200 samples from more than eighty sites was that the overall angular standard deviation for both the directions and the virtual geomagnetic poles is only 7.5° , which is much lower than the value to be expected from secular variation models. Of course, this result could be taken at face value; and the conclusion would be that the palaeosecular variation was anomalously low. But at least one other feature on the overall data suggests that there is more in it than that. Cleaned directions from all but one of the sites fall into distinctly normal and reversed groups, but the mean normal and reversed directions differ not by 180° but by 169° with an error of 2.4° . In short, the two mean directions are not antiparallel, which implies that the sampling may not have covered the full range of field variations.

This view is supported by more detailed analyses of data subsets. For example, for the Mammoth event data the precision parameter between sites is effectively infinite—which means there is no detectable dispersion in the direction from the twelve relevant sites. In this case it would appear that the interval of eruption was too short for even a part of the full range of palaeosecular variation to be recorded. This is confirmed by the geology (the lack of tuff, boles or evidence of erosion at the flow surfaces) and by the close grouping of potassium-argon ages. In the case of the Matuyama epoch lavas the angular standard deviation is somewhat higher (5.3° compared with 3.8°), but again the geology and radiometric dating suggest a short eruption interval (less than 0.10×10^6 yr). For the Gauss epoch lavas the angular standard deviation is higher at 7.1° and sampling seems to have covered a range of 0.35×10^6 yr, but the scatter is still much lower than that predicted by

models. Quite apart from the independent evidence for short eruption intervals from the Mammoth and Matuyama lavas, the validity of attributing all the low angular standard deviations to too short sampling periods is supported by the fact that the mean virtual geomagnetic pole is 14° from the rotational pole. To explain this in terms of continental drift, for example, would imply drift rates at least an order of magnitude higher than usual.

So Aziz-Ur-Rahman and McDougall conclude that the Norfolk-Philip angular standard deviations are low because the full range of palaeosecular variations has not been sampled. On the face of it, there is nothing spectacular about this at all—incomplete sampling is an occupational hazard in this type of work. The fact is, however, that the total interval sampled on the Norfolk and Philip Islands is about 0.7×10^6 yr (comparable with the whole length of the Brunhes) and both normal and reversed rocks are included. In other words, the time covered is much longer than the estimated periodicities of secular variations and yet the estimated palaeosecular variation is still not valid.

This leads Aziz-Ur-Rahman and McDougall to question the validity of all previous studies—and particularly those from Hawaiian rocks—for which the sampling interval seemed at the time to be sufficient. For example, many of the individual Hawaiian lava sequences investigated were erupted over periods of thousands to tens of thousands of years at various points in the Brunhes report. In view of the Norfolk-Philip results, can the low angular standard deviations observed in the Hawaiian rocks still be regarded as valid estimates of palaeosecular variation? And, if so, is the supposed central Pacific field low genuine?

EARTH'S PARTICLES AND FIELDS

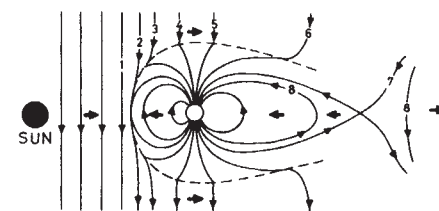
Magnetospheric Energy

from a Correspondent

THE occurrence of the aurora, magnetic storms and many other natural phenomena is greatly influenced by the interaction of the Earth's magnetic field with the charged particles of the solar wind. This interaction, which gives rise to the magnetosphere (the region of space where the Earth's magnetic field has controlling influence), has been under critical review at a conference on the Earth's particles and fields held in Sheffield from August 13 to 24.

It was reported that many of the data on the Earth's magnetic field and the plasma within it, which have been accumulated by rockets and satellites, increase support for the open convective or reconnection model of the magnetosphere.

In the reconnection model, the Earth's magnetic field lines take the form shown in the diagram due to the action of the solar wind. The solar wind carries with it ("frozen-in") the interplanetary magnetic field (IMF) which, when pointing in a southward direction, can connect with the Earth's field at the front of the magnetosphere, peel off field lines and carry them downstream to form a tail. So that the magnetic flux content of the tail does not increase indefinitely, the model requires that field lines reconnect in the tail and are convected back to the sunward boundary of the magnetosphere.



Reconnection model of the Earth's magnetic field.

The model can be understood by reference to the diagram in which successive numbers indicate the motion of the field lines and the solid arrows give the direction of convective plasma flow. An interesting feature of the model is that the field lines in the polar cap regions are open and connected to the interplanetary magnetic field. At the point of reconnection in the tail an X-type neutral line is formed where the magnetic field is cancelled.

The general picture of the magnetosphere is reasonably clear. What has been in doubt for many years is the means by which particles are injected into and/or are energized within the magnetosphere. The injection of energy is now thought to occur during magnetospheric substorms. The substorm manifests itself through perturbations in the Earth's magnetic field and the behaviour of auroral forms.

The identification of a substorm from ground-based magnetograms was shown by Dr G. Rostoker (University of Alberta) to be a complex problem involving the analysis of data from many high altitude stations. It is particularly difficult to assign a precise time to the beginning of the substorm.

The essential feature of the substorm is that it corresponds to an explosive dissipation of energy at high latitudes which is associated with the breakup of auroral displays and the flow of currents in the ionosphere which perturb the Earth's magnetic field. A substorm typically lasts for about an hour and results from the sudden release of magnetic energy which is stored in the tail. The mechanism by which the energy is released is not understood, but the competing theories are a discharge process occurring at the X-type neutral line or

instabilities occurring in the same region of the tail.

The chief bar to progress in studying substorms is the difficulty of unravelling the complex magnetic data to identify them and their starting time. It has been established that the auroral electrojet index, which is a measure of currents flowing in the auroral ionosphere, is unreliable for this purpose. Most workers concede this difficulty, the exception being C. McIlwain of the University of California, San Diego, who claims to be able to establish the beginning of a substorm to an accuracy of plus or minus five minutes and to have done so for over 3,000 substorms. The basis of McIlwain's method is that the magnetospheric substorm corresponds to a sudden intensification of the electric fields in the magnetosphere which in turn produce an increase in the particle populations in the tail sector. These particle enhancements are reported by McIlwain to be clearly seen in the data acquired from the geosynchronous satellite ATS 5. Clearly important work will follow when the timings and details of these substorms are released.

Although much of the conference was devoted to the Earth's magnetosphere, Drs F. M. Neubauer (Technical University, Branschweig), N. Brice (Cornell University) and J. Warwick (University of Colorado) reported work on Jupiter's magnetosphere. Jupiter has a magnetic field which is about 10 gauss at the surface and gives rise to a much larger magnetosphere and associated radiation belts than those of the Earth. Estimates of the position of the forward boundary of the Jovian magnetosphere put it at a distance of about 50 Jupiter radii, compared with a distance of 10 Earth radii for the forward boundary of our magnetosphere.

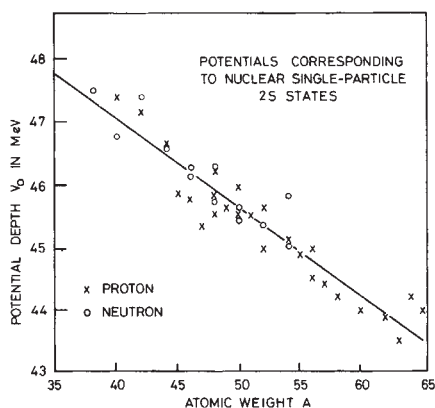
NUCLEAR STRUCTURE

Single-particle States

from a Correspondent

ACCORDING to the independent particle shell model each nucleon in the nucleus moves in its own orbit, characterized by definite quantum numbers, and its spatial distribution is given by its wavefunction. The orbits are filled starting from those of lowest energy and subject to the Pauli principle that no two particles can have the same quantum numbers. This gives the familiar sequence of nuclear states: $1s_{1/2}$, $1p_{3/2}$, $1p_{1/2}$, $2s_{1/2}$, $1d_{5/2}$, $1d_{3/2}$ and so on. When a state is completely filled with neutrons and protons a nucleus of exceptional stability is formed, and this naturally gives the shell structure and associated "magic" numbers of neutrons or protons.

The stable structures formed by magic



Potentials fitted to individual 2s hole states compared with the average value. The dependence on the nuclear symmetry parameter has been removed using the best value of the corresponding term in the potential.

numbers of neutrons and protons are hardly disturbed when a single nucleon is added to them, so that the properties of such nuclei are in many respects those of a single nucleon coupled to a relatively inert core. The low-lying states are just those expected from the simple shell model, and the occupancy of the orbit as measured by a nucleon transfer reaction is close to unity. Nuclei with one particle less than a closed shell also show these single-particle states, as they are called.

If additional nucleons are added or taken away from such nuclei the nucleons outside the core can couple together in many ways, giving much more complicated sequences of nuclear levels, and the simplicity of the model is lost. The single-particle states are each split into a number of fragments, spread over several million electron volts of excitation energy. It has, however, recently been found by Millener and Hodgson (*Nucl. Phys.*, **A209**, 59; 1973) that if the centroid of the fragmented state is calculated by weighting the energies of the fragments by their strengths as determined by one-nucleon transfer reactions, then these centroid energies behave in a systematic way from one nucleus to the next, even far away from the closed shells. This shows that the forces which fragment the states are unable to change their centroid energies significantly.

It is possible to obtain these energies as eigenvalues of a simple one-body potential similar to the real part of the optical potential used to describe the elastic scattering of nucleons by nuclei. The depth of the potential depends linearly on the nuclear symmetry parameter $(N-Z)/A$ and on A itself. Each state can be followed from nucleus to nucleus across the periodic table until ultimately it is at too high or too low an energy to be measured accurately. The optimum parameters of the potential can thus be determined for each state

individually and the state dependence is found to be quite small.

The optimum single-particle potentials give energies for the centroids of the single-particle states that agree with the experimental values to within about 0.2 to 0.3 MeV, which is comparable to the accuracy of the experimental measurements. The consistency between the potentials fitted to each state and the best fit potentials is shown for the 2s hole states in the figure, and similar results are found for the other states.

These potentials can be used to calculate the wavefunctions of all the nucleons, and by summing their squared moduli $|\Psi|^2$ one can obtain the nuclear matter and charge distributions. The latter can be checked against the accurate values obtained from analyses of the elastic scattering of electrons by nuclei, and the agreement is within the experimental uncertainties.

PLANT TAXONOMY

New World Bamboos



ON April 15, 1970, Floyd A. McClure died at work in his bamboo garden while removing a plant to give to a young friend. Before his death he had almost completed a revision of the genera of New World bamboos; T. R. Soderstrom, a colleague of McClure's at the Smithsonian Institution, was fortunately able to complete the work and it has now appeared—with descriptions of seventeen genera, including four new genera and species—in the series *Smithsonian Contributions to Botany* (No. 9; 1973). This figure shows the form and parts of the type species, *Swallemochloa subtessellata*, of one of the new genera.

Training Science Teachers in Methodology

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This article describes the philosophy behind and the problems involved in developing a curriculum appropriate to the training of science teachers in methodology.

THE average prospective science teacher will normally have completed two years in a secondary school sixth form or its equivalent, and three years of degree studies, before embarking on a single year of postgraduate professional training. There is a view, unfortunately accepted by many people, that teaching is intuitive and inborn and this must inevitably produce a clash of cultures—for how can a scientist after five years of concentrated scientific thought expect to change his attitudes overnight?

There are, however, fortunately many people who do not accept this non-scientific appraisal of teaching, and who believe that it must be approached analytically. According to Taba¹, curriculum is a way of preparing young people to participate as productive members of our culture and thus, if these prospective teachers are to approach their chosen career analytically, their training course must be designed to show them the essential elements. It is thus necessary to investigate the initial problems of curriculum development before designing a curriculum to meet the needs of these potential science teachers.

The splits which exist in the literature^{2,3} devoted to curriculum development are very obvious. Child-centred, society-centred and subject-centred curricula are vying with each other as the exclusive approaches to the entire curriculum. The statements issued of the advantages and disadvantages of each seem to set these patterns into a sharper contrast than they merit.

The confusion that at present still exists in curriculum making has many sources. (a) There is a lack of clarity and conflicts in the basic sciences from which education draws its data and guiding principles. (b) There is no single theory regarding the nature of the individual or the nature of learning. (c) There is a lack of awareness of the goals of our culture and the role of the individual in that culture.

A great deal of confusion has arisen from the fact that no coherent theory of learning exists and even what is known about learning has not been clearly brought together when applied by curriculum makers. This is clearly seen when, for example, the stimulus response theory is applied in some teaching and the field theory in other cases without differentiating the particular aspects to which they are relevant.

To make proper use of the intellectual talent available to the teaching profession a theory of curriculum development appropriate to their training is needed. Such a theory should not only define the problems with which the curriculum development must deal, but also elaborate the system of concepts which must be used to assess the relevance of these data.

All curricula, no matter what their particular design, are composed of certain echelons. A curriculum must commence with a statement of aims and of specific objectives, it must indicate some selection and organization of content and it either implies or manifests certain patterns of learning and teaching. Finally, it must include an element of evaluation of the outcomes.

Inevitably curricula will differ according to the emphasis given to each of these echelons, and according to the basis on which the decisions regarding each are made.

The curriculum development task requires orderly thinking—one needs to examine both the order in which decisions are made and the way in which they are made to make sure that all relevant considerations are brought to bear on these decisions. The order and elements of a curriculum model⁴ appropriate to a postgraduate science teacher's methodology course are illustrated in Fig. 1. The intimate nature of the elements, the relative emphasis placed on each and the difficulties encountered should become clear when the model is applied to specific items appropriate to science teacher training.

Aims and Objectives

An educational programme, like any activity, is directed by the expectations of certain outcomes. The chief activity of education is to change individuals in some way: to add to the knowledge they possess, to enable them to perform skills which otherwise they would not perform, and to develop certain understandings, insights and appreciations. Chapman⁵ has attempted to analyse the educational processes appropriate to the education of graduate physics teachers, and with minor modifications they could be equally appropriate to all scientific disciplines. We are, however, at present considering educational aims, and although providing a philosophy of education these are only a step towards translating the needs⁶ and values of society and individuals into an education programme. To be of any value educational aims need transforming into educational objectives.

The chief function of the more specific platform of objectives is to guide the making of curriculum decisions. Perhaps the most important guiding is that of decisions about the selection of content and of learning experience, and of providing criteria on what to teach and how to teach it. Because the possibilities of knowledge and learning are boundless there is always the problem of selection. A platform of desired objectives supplies a criterion for these decisions.

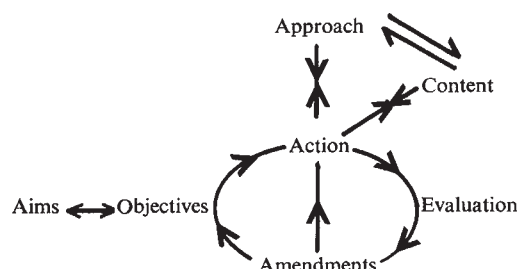


Fig. 1 Order and elements of a curriculum model.

To illustrate this part of the model we shall consider some of the many aims that are likely to be included when considering the course in question, namely, (a) to produce good science teachers; (b) to foster an acceptance of cognitive, affective and psychomotor objectives in the teaching of science; (c) to develop the necessary skills essential to a science teacher.

The first of these aims is obviously a blanket statement of intent for the whole course, and should be regarded as a primary aim. It inevitably has many facets and requires further expansion into secondary aims before beginning the task of considering the educational objectives. Aims (b) and (c) now fall into this class of secondary aims: they are still far too vague but they do indicate the approximate areas from which the more detailed objectives can be drawn.

These three aims illustrate the difficulty that may be experienced in constructing a list of specific objectives. Bloom *et al.*⁷ have produced hierarchies of objectives which may be appropriate in the cognitive domain but leave much work to be completed in the affective and psychomotor domains. It may well, in the context of a science teacher training course, be advisable to leave aim (b) as it is and consider it as an intermediate objective or statement of intent. In doing this one hopes that the philosophy behind it will pervade the specific objectives produced from the other aims.

The third aim is much easier to expand. These skills can be isolated—they include, for example, organizing ability, appropriate use of educational technology, and ability to assess apparatus. Having identified the relevant skills it is comparatively easy to construct a list of appropriate objectives. An example of one such objective could be to be able to assemble, use and service a set list of audiovisual aids. From this specific objective it is possible to develop criteria necessary for evaluation and thus estimate the effectiveness of the original aim.

This part of the curriculum development is very difficult and very time consuming. It is, however, essential if a worthwhile course is to be produced. The chief difficulty is in crystallizing the broad statements of intent into specific behavioural objectives, in particular aims related to the affective domain. Very often a compromise will have to be sought—translating those general objectives into specific objectives wherever possible, but leaving many as general statements of intent.

Action, Approach and Content

If the curriculum is to be a plan for learning, its content and learning experiences need to be organized so that they serve the educational objectives. Often the curriculum is ineffective not because its content is inadequate but because it is put together in a way that makes learning difficult, or because learning experiences are organized in a way that makes learning either less efficient or less productive than it might be.

During the past few years the organization of content has received a good deal of attention, whereas relatively little theoretical thinking has been devoted to the problem of organizing the learning experiences. Consequently the course should offer the list of subjects and topics to be covered and also the sequence which will lead to the most efficient learning situation. The discussion of the model of Fig. 1 must thus include the action-approach-content component as a single item, since each is intimately related to the other two.

The specific objective referred to in the preceding section related to the audiovisual aids can now be examined in more detail. Specifying the areas assembly, use and service, precisely determines the content but not the approach. The approach is governed by the criterion that it should produce the most efficient learning situation. It may be decided that the assemble and service aspects can be approached most efficiently in small group seminar-practical sessions, whereas the use aspect is best dealt with in the school situation. Thus

having stipulated the content and the approach, the action can be determined.

From this example it may be seen that this component of the model is reasonably easily applied when the original objective is specific. Difficulties arise when the objective has had to be left as a general statement. If we consider the earlier statement regarding fostering an acceptance of cognitive, affective and psychomotor objectives in the teaching of science, we have no clear indication of how we are to judge the end product and thus little information on which to base our action. This should not be regarded as an excuse for not attempting to implement the original rather vague objective. It may mean that we have to rely on hunches or intuition when applying this component of the model to it.

Evaluation

The nature of the evaluation programme depends, first, on what objectives are pursued and how each objective is defined and, second, on the purposes for which the results of the evaluation are to be used. The more comprehensive and complex the objectives the more complex the task of evaluation. For the rather vague general statements it may be simply a rendering of a value judgment based on sheer opinion. The methods of evaluation, in fact, include any way of securing valid evidence on attainment of objectives. Since the curriculum is essentially a plan for helping students to learn, ultimately all evaluation goes back to the criteria of effectiveness of learning.

On first impressions, evaluating the objectives dealing with audiovisual aids would appear to be straightforward. Superficially it is possible to say whether the students can fulfil the conditions stipulated by the objective, but unless criteria are established on which the evaluation is to be based, it will be impossible to allow for varying standards of performance. Unless specific criteria are stated the judgments will remain impressions and one of the advantages of having specific objectives will be lost.

The second objective was rather vague and hence will have to be evaluated by value judgments. This particular example has the advantage that it can be judged on many occasions while the student is in a classroom situation on teaching practice and the final evaluation will be a composite rather than a single one. The obvious danger of having to rely on impressions for evaluation arises when these impressions have to be given in a single, isolated situation.

Care must be taken to differentiate between assessing the student and assessing the course, since invariably most objectives do in fact have to be judged in terms of the students' performances. A student can be assessed in terms of a single objective, whereas an objective must not be judged in terms of a single student. Before a final verdict is given on any objective the performance of all the students must be considered, and the difficulty then arises as to the criteria for acceptability or rejection.

The evaluation of the many different objectives associated with the course has the added advantage of encouraging a more diagnostic assessment of the student. With the wealth of information that this built-in evaluation process produces, there is no need or justification in reducing the achievements of the student to a single mark.

It is important that the evaluation programme yields an objective and valid picture of the achievement. This means that the data on which the evaluation is based should be reasonably free of subjective bias or other deficiencies which mar their objectivity and accuracy. If this is not the case it will be impossible to say which component of the model requires amending. If we are quite satisfied with the evaluation techniques and results, the amendments can only apply to the action or the objectives.

If the evaluation reveals that amendment is desirable, the

most efficient approach is to progress through the model in reverse—inspecting the action first and only moving on to the objectives and finally the aims when the component in question appears satisfactory. By adapting this procedure it should be possible to make minor modifications without running the risk of inadvertently removing satisfactory material which could be the case by beginning the amendment procedure with the initial aims.

A one year training course such as the one under discussion also requires a different type of amendment, namely the possibility of completely reorientating the training at a later stage. It is obviously reasonable to structure the first part of the course when developing the basic skills appropriate to teaching, but this will not necessarily reflect the interests of the students or the needs of their first appointment.

This appointment is very often made approximately halfway through the course and so the optimum arrangement is to have a closely structured beginning moving towards a very much more open-ended situation as the course develops. This continuous amendment also has the added advantage of letting the students see this analytical approach in practice and so should encourage them to adapt it in their own teaching.

The foregoing discussion illustrates the possibility and problems associated with developing a curriculum appropriate to the training of potential science teachers. It is imperative that the students are made aware of what constitutes the scientific method as well as the need for an analytical approach to their own training and hence to their own teaching if their pupils are to realize the impact science has on the culture and life of our society. The discussion has been limited to science methodology courses but there is no justification in placing this restriction on it, and it is our hope that all subject method tutors will investigate its applicability to their own particular disciplines.

¹ Taba, H., *Curriculum Development Theory and Practice* (Harcourt, Brace and World, New York, 1962).

² *The Curriculum: Content, Design and Development* (edit. by Hooper, R.) (Oliver and Boyd, 1971).

³ Mackenzie, N., Erant, M., and Jones, H. C., *Teaching and Learning: An Introduction to New Methods and Resources in Higher Education* (UNESCO, Paris, 1970).

⁴ *Schools Council Integrated Science Project 1970*, Bulletin No. 1.

⁵ Chapman, B. R., *Phys. Ed.*, 6, 376 (1971).

⁶ *Education: A Framework for Expansion*, cmdnd 5174 (HMSO, 1972).

⁷ Bloom, B. S., *Taxonomy of Educational Objectives: Handbook 1* (Longmans, London, 1956).

Seismic Activity, Polar Tides and the Chandler Wobble

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Earthquakes may be triggered by changes in the elastic energy which are neither too fast ($\sim$ days) nor too slow ($\sim 10^6$ yr). Such a point of view provides a qualitative understanding of suggested correlations between polar motion and the annual seismic energy release. The Chandler wobble and earthquakes may have a common excitation source—the release of elastic energy stored in the Earth—and we show that a resonant coupling between seismic activity and polar motion has the right sign and strength to explain the pumping of the Chandler wobble as a consequence of in-phase release of elastic energy.

WE have recently carried out a calculation of the global quadrupolar mechanical energy stored in the Earth, with the aid of a model which relates the various terms in a spherical harmonic expansion of the elastic strains to the observed lithospheric configuration¹. The overall quadrupolar energy

content was found to be $\sim 10^{32}$ erg, some of which results from misorientation between the rotation axis and the elastic reference axis. That is sufficiently large that one may reasonably expect this energy to play an important role in various physical processes in the crust and mantle, including polar wandering, the Chandler wobble, and seismic activity.

Elastic Energy Content and Seismic Activity

Even in isolation, the crust and mantle of the Earth will tend to lose their elastic energy content in rheological fashion; however, such changes occur very slowly (over time scales $\sim 10^8$ yr) and are not likely to result in the occasional sudden release of elastic energy characteristic of earthquakes. Of course the crust and mantle of the Earth are not isolated, but are subject to the external gravitational torques of the Moon and Sun, as well as to internal torques associated with core-mantle coupling and polar motion. The resulting lunar, solar and polar tides cause corresponding periodic variations in the elastic energy, which may substantially enhance both continental drift and seismic activity, in much the same way as shaking a box of pebbles enhances the rate at which they reach a state of minimum potential energy. It is natural to inquire whether there might be some correlation between the essentially reversible variations in the elastic energy and the seismic activity, which corresponds to an irreversible decrease in the elastic energy content of the Earth. In other words, are there periodic variations in seismic activity which are related to periodic variations in the elastic energy?

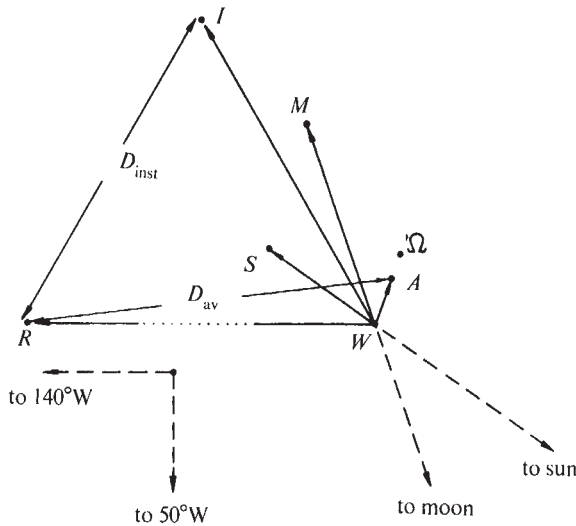


Fig. 1 Construction of the position of the inertia pole, I , from the positions of the rotation pole, Ω , the Moon and the Sun. The diagram, which is not to scale, depicts a plane tangent to the Earth at the nutation pole, W . WA , WM , and WS are, respectively, the effective vector contributions of these sources of tidal distortion and WI is their vectorial sum. D_{inst} is the instantaneous distance in the plane, between I and the reference pole R ; D_{av} is the same distance averaged over the daily lunar and solar tides, and thus changes only with the (slower) motion of the rotation axis.

There is, as yet, no evidence of any global correlation between seismic activity and daily lunar and solar tides². There does exist, however, evidence for periodic variations in seismic activity on a longer time scale. Whitten³ has called attention to a quasi-periodicity of 7 yr in the total seismic energy release from earthquakes, and has suggested that such a periodicity may be related to the polar motion. Myerson⁴ has pointed out the possible existence of a 40 yr periodicity in the yearly count of large magnitude (≥ 7) earthquakes. On a still longer time scale, Wilson⁵ has reported a possible 370 yr periodicity, determined by Chinese scholars from a study of ancient earthquake records. Assuming that such regular variations do occur (and their existence is far from well established), and that comparable periodic variations can be found in the elastic energy (and we shall show that this is the case), one is then led to inquire as to whether there exist physical mechanisms which couple seismic activity to elastic energy variation. The misorientation of the rotation and elastic axes provides just such a mechanism.

To calculate the periodic variations in the elastic energy associated with lunar, solar, and polar tides, we use essentially the same approach as that developed earlier for calculating its time-averaged "static" value¹. We thereby implicitly assume that the dynamic quadrupolar response of the inertial tensor of the Earth differs little from its static response. The calculation is carried out with the aid of the vectorial construction shown in Fig. 1, which is a view of the Earth from Polaris, with W representing the pole of the traceless part of the nutation tensor δI_w (ref. 1) and Ω the instantaneous rotational pole. The points A , S , and M , represent the contribution to the pole I (of the traceless total inertial tensor δI), of the quadrupolar potentials associated with rotation, the Sun and the Moon, respectively. The point R represents the pole of a traceless reference tensor, δI_R , defined in such a way that the time varying portion of the quadrupolar part of the elastic energy of the Earth may be written as

$$E_{el} = 2/3 \ B T_r \ (\delta I - \delta I_R)^2 / I_0^2 \quad (1)$$

From Fig. 1, the elastic energy becomes

$$E_{el} = B \ [(\epsilon - \epsilon_R)^2 + 3\epsilon\epsilon_R \ (D^2/R_0^2)] \quad (2)$$

where ϵ and ϵ_R are the oblateness parameters associated with δI and δI_R respectively, B is the elastic energy coefficient, R_0 is the Earth's radius and D , the distance in the polar plane between R and I , provides a direct measure of that part of the elastic energy which arises from an angular mismatch between δI and the reference tensor δI_R . From ref. 1, we have $\epsilon = 2.16 \times 10^{-3}$, $\epsilon_R = 1.88 \times 10^{-3}$, and $D \approx 180$ km. Because $B = 1.34 \times 10^{39}$ erg, this angular mismatch gives rise to an elastic energy of $\sim 1.3 \times 10^{31}$ erg, some 10% of the overall elastic energy stored in the Earth. As emphasized in ref. 1, this is substantially higher than values previously cited for the angular elastic energy, because those estimates were based on the unjustified assumption that $\delta I_R = \delta I_w$.

The construction in Fig. 1 is not to scale, because the time varying portion of the angular part of the elastic energy is much smaller than 10^{31} erg. Thus, WA provides a measure of the amplitude of the polar motion, and is typically ~ 6 m; $|WM|$ is, on average, some thirty times larger than $|WA|$ (and six times larger than $|WS|$), and it is the Moon which makes the dominant contribution to the instantaneous position of the pole, I , as measured relative to the centre of nutation, W . On the other hand, if one averages over a period of a few days, it is only WA which survives, because the positions of the points M and S change daily.

The slower variations in the elastic energy arise chiefly from the polar tides and have periods determined by the polar motion. A detailed account of periodic polar motions can be found in Munk and MacDonald⁶; the most important are: an annual term, which arises from atmospheric circulation; and the Chandler period, of 437 ± 2 d, which corresponds to the Eulerian motion of Ω .

In addition, one may have: a 24 yr libration, with an amplitude of 0.02 arc s along the 58 W–122 E meridian, as suggested by Markowitz⁷, and a variation in the amplitude of the Chandler motion which is periodic with a period of 40 yr; this may originate in a splitting of the Chandler frequency, produced by interlayer coupling in the mantle⁸.

Because the period of the latter two variations is of the order of the length of the data chains from which they have been extracted, their identification as well defined periodicities must be regarded as tentative; in any event, their amplitude is small compared to the annual and Chandler contributions. We may therefore write

$$\hat{A} \approx A_a \exp[i(\omega_a t + \phi_a)] + A_p \exp[i(\omega_p t + \phi_p)] \quad (3)$$

where A_a , ω_a and A_p , ω_p , are the amplitudes and frequencies of the annual and Chandler terms. On making use of Fig. 1, we obtain

$$D^2 = R^2 + 2RA_a \cos(\omega_a t + \phi_a) + 2RA_p \cos(\omega_p t + \phi_p) + 2A_a A_p \cos[(\omega_a - \omega_p)t + (\phi_a - \phi_p)] \quad (4)$$

Thus there are variations in the elastic energy of frequency ω_a , ω_p and (with a negligible amplitude) $\omega_a - \omega_p$. In Table 1 we give the relative amplitudes of the time varying terms, as well as the corresponding amplitudes for the Sun and Moon and the periodic variation in the elastic energy which comes from the suggested 40 yr periodic variation in A_p .

In a rheologically young planet, we expect that quakes will occur whenever the total elastic energy in a certain region exceeds some critical value⁹. But in a rheologically old planet like the Earth, we expect that the strain energy is always near its critical value, because global changes in the elastic energy in a given year coming from seismic activity, continental drift, or external forces are small compared to the total elastic energy reservoir of $\sim 10^{32}$ erg. In these circumstances, it seems plausible that the effectiveness of tidal variations in triggering elastic energy release will depend both on the magnitude of the variation and on the time scale over which

the variation takes place. Release of elastic energy involves surmounting potential barriers which, in a rheologically old planet, depend substantially upon local conditions. It follows that if the period of an elastic energy variation is too short, there may not be sufficient time during that period for the matter in given regions to surmount its local potential barriers, so that the corresponding amplitude is ineffective in bringing about energy release.

This working hypothesis is embodied in the following simple functional relation between the irreversible rate of change of the elastic energy, E_{el} , and the reversible time-varying elastic energy

$$\left. \frac{\partial E_{el}}{\partial t} \right|_{irr} = F\left[\int_0^t d\tau f(t-\tau)E_{el}(\tau)\right] \equiv F[y] \quad (5)$$

Here F is a function of y , the time-weighted storage of elastic energy, and we assume that $F[y] < 0$ and $dF/dy > 0$; f is a memory function which permits one to take into account the possible influence of changing local conditions on the local energy release; thus one might have $f \sim \exp(-\beta t)$ where β^{-1} is the appropriate "memory" time constant, or f may be a step function with a cutoff at a time T . In the absence of any external forces, and for small y , one gets an exponential reduction in the elastic energy; for a component of E_{el} which varies at frequency Ω , the amplitude of its effectiveness in inducing a change in E_{el} is multiplied by Ω^{-1} , so that rapid reversible variations in E_{el} may turn out to be far less effective than slow ones.

Table 1 Maximum Amplitudes of Tidal Angular Elastic Energy Changes

	Periodicity	Amplitude (10^{26} erg)	Period $\times$ amplitude (10^{28} erg d)
Lunar tide	Daily	70	0.7
Solar tide	Daily	10	0.1
Chandler wobble	437 ± 2 d	1.3	5.7
Annual polar motion	Yearly	1.1	4.0
Chandler "40 yr" periodicity	Near 437 and 365 d	0.9	~ 3.6
Annual-Chandler interference	6-7 yr	4×10^{-5}	7.8×10^{-4}

From Table 1, we see that if it is the amplitude divided by the frequency which is the relevant one for seismic energy release, then in spite of their large amplitudes the lunar and solar tides are ineffective when compared to the polar tides. We further note that according to this criterion, it is the Chandler and annual components which emerge as the most effective in inducing irreversible energy release and seismic activity; their combined contribution to y , the time-weighted storage of elastic energy in equation (5), is

$$(2RA_a/\omega_a) \sin(\omega_a t + \phi_a) + (2RA_p/\omega_p) \sin(\omega_p t + \phi_p) \quad (6)$$

Because the function $F[y]$ in equation (5) is probably highly non-linear, strong maxima in the irreversible elastic energy release are to be expected principally at the largest maxima of equation (6). For example, if $\phi_a = \phi_p$, and $\omega_a/\omega_p = 1.2$ exactly, absolute maxima (of 9.7×10^{28} erg d) will occur whenever $\omega_a \Delta t = 2n\pi$ and $\omega_p \Delta t = 2m\pi$, that is, when Δt is a multiple of $12\pi/\omega_a = 10\pi/\omega_p$, corresponding to a 6 yr period. In this case, $\omega_a - \omega_p$ is 6 yr as well, so that under these special circumstances the sum of the annual and Chandler terms would mimic an interference effect; the size of the effect is, however, some four orders of magnitude larger than one gets from the usual interference term.

In reality, ω_a/ω_p is not an exact ratio of small integers, so that the corresponding seismic activity would be expected

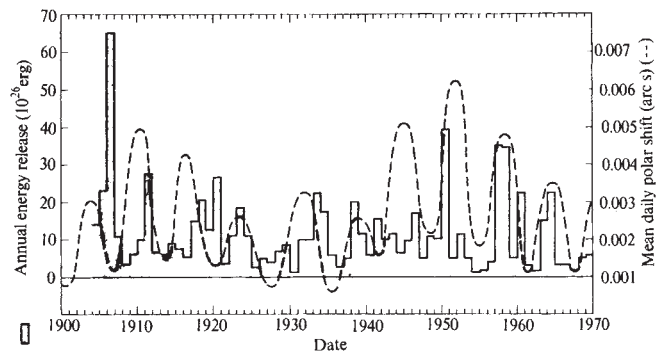


Fig. 2 Whitten's proposed correlation between seismic activity and polar motion. Note that the current energy estimates may differ.

to correlate only roughly with the 6 to 7 yr period of the interference between the annual and Chandler terms. This quasi-periodic seismic activity may well correspond to the 7 yr periodicity suggested by Whitten, whose analysis is reproduced in Fig. 2.

Although the existence of a Chandler "40 yr periodicity" is far from well established, if we assume that such a periodicity exists, the corresponding variations in the elastic energy would seem to have the right amplitude (and frequency) to explain the 40 yr periodicity in large earthquake seismic energy release proposed by Myerson.

Excitation of the Chandler Wobble

We have argued that "reversible" changes in the elastic energy associated with polar motion can trigger irreversible elastic energy release; we now explore the inverse possibility, that some fraction of this elastic energy release may serve to excite the Chandler wobble in the sense of providing the energy dissipated in frictional irreversible polar tidal processes which act to damp that wobble. That an excitation mechanism is needed has long been recognized; the persistence of the amplitude of the Chandler wobble over the period of more than 50 yr of modern observations, essentially without any noticeable change (except for the possible 40 yr quasi-periodicity) requires that energy be supplied at the frequency of the Chandler component of the polar motion. Earthquakes were suggested as early as 1907 as a possible excitation mechanism¹⁰ and this suggestion has recently been revived by Smylie and Mansinha^{11,12}, who consider the energy transfer which takes place as a result of random jumps in the centre of nutation associated with major earthquakes. Detailed calculations¹³ have shown that such a random excitation mechanism is clearly not enough, even though it may cause partial excitation; large earthquakes are too infrequent to sustain the observed Chandler amplitude. A further argument against this being the only mechanism is that one has thus far not observed large cusps in the polar path, associated with jumps in the centre of nutation which carry it out of the previous wobble circle. Such jumps would be expected if there is a relation between the overall amplitude of the polar motion and the average quake-induced jump in the centre of nutation.

A resonant coupling between seismic activity and polar motion is free of the above objections; such coupling is a natural consequence of the physical picture we have developed, in which Chandler wobble and earthquakes have a common excitation source—the release of elastic energy stored in the Earth which is, in turn, triggered by the physical processes which produce the observed polar motion. We here describe briefly the origin of such a resonant coupling, and show that it has the right sign and strength to permit elastic energy release to pump the Chandler wobble at about its current amplitude.

According to our picture of a rheologically old Earth,

and perhaps to solid stars as well. Thus any planet which has substantive surface features may be expected to have an appreciable reservoir of elastic energy, including an angular term arising from a misorientation of its rotation and elastic axes. Under these circumstances free precession of the planet (or star) is likely to occur in such a way that resonant coupling between the indirect seismic activity and polar motion acts to pump that precessional motion. In view of its prominent surface features, Mars would seem an especially promising candidate for such a planetary wobble.

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Erratum

In the article "Quadrupolar Analysis of Storage and Release of Elastic Energy in the Earth" by D. Pines and J. Shaham (*Nature phys. Sci.*, **243**, 122; 1973), equation (4) should read:

$$\delta I_{\Omega} = I_0 \epsilon_{\Omega} (3n_{\Omega} n_{\Omega} / 2 - e/2)$$

Equation (7) should read:

$$\delta I_{\mu} = I_0 \epsilon_{\mu} (3n_{\mu} n_{\mu} / 2 - e/2)$$

Equation (8) should read:

$$\delta I_{\mu} = \epsilon_{\mu} (3n_{\mu} n_{\mu} / 2 - e/2) + \eta_{\mu} (I_{\mu} I_{\mu} - m_{\mu} m_{\mu})$$

Line 5, column 7, Table 1, should read [0.933, 0.217, -0.337]. In both parts of Fig. 2 the angle between n_R and n_C should be 2° and not 0.2° .

Preliminary Characterization of Two Species of dsRNA in Yeast and their Relationship to the "Killer" Character

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Two high molecular weight dsRNA species have been found in yeast and strains have been found which possess either the larger, or both, of these molecules. From genetic evidence, we conclude that, together, these two dsRNAs determine the cytoplasmically inherited killer character.

THE occurrence of high molecular weight double stranded (dsRNA) in some strains of the yeast *Saccharomyces cerevisiae* was reported recently by Berry and Bevan¹, and confirmed by Vodkin and Fink². The molecule was discovered during a search for the genetic determinant of the cytoplasmically inherited "killer" character³⁻⁶, and was characterized as dsRNA mainly on the basis of its nuclease resistance. We now wish to confirm that characterization,

to report the occurrence of a further species of dsRNA and to correlate its presence with the killer character.

Total nucleic acid was prepared by first disrupting the cells with an Eaton press⁷ and using the phenol method of Kirby and Parish⁸. Sodium *tri*-isopropyl-naphthalene-sulphonate (TNS) was used as a detergent in the aqueous phase of the extraction. The change to this detergent abolished the breakdown of rRNA in extractions from killer strains reported by Berry and Bevan¹. When total nucleic acid was extracted for the bulk isolation of dsRNA the cells were not passed through the Eaton press but were subjected to a cycle of freezing and thawing in TNS buffer before phenol extraction. This method yielded DNA, tRNA and dsRNA but gave little rRNA and thus simplified the subsequent separation.

Isolation of the dsRNA was achieved by CF11 chromatography⁹. The nucleic acid was first dissolved in 0.15 M sodium acetate buffer, pH 6.9, and spun at 15,000g for 1 h to remove high molecular weight polysaccharides¹⁰. Transfer RNA was removed by permeation chromatography of the supernatant using a 40×2.2 cm column of Corning

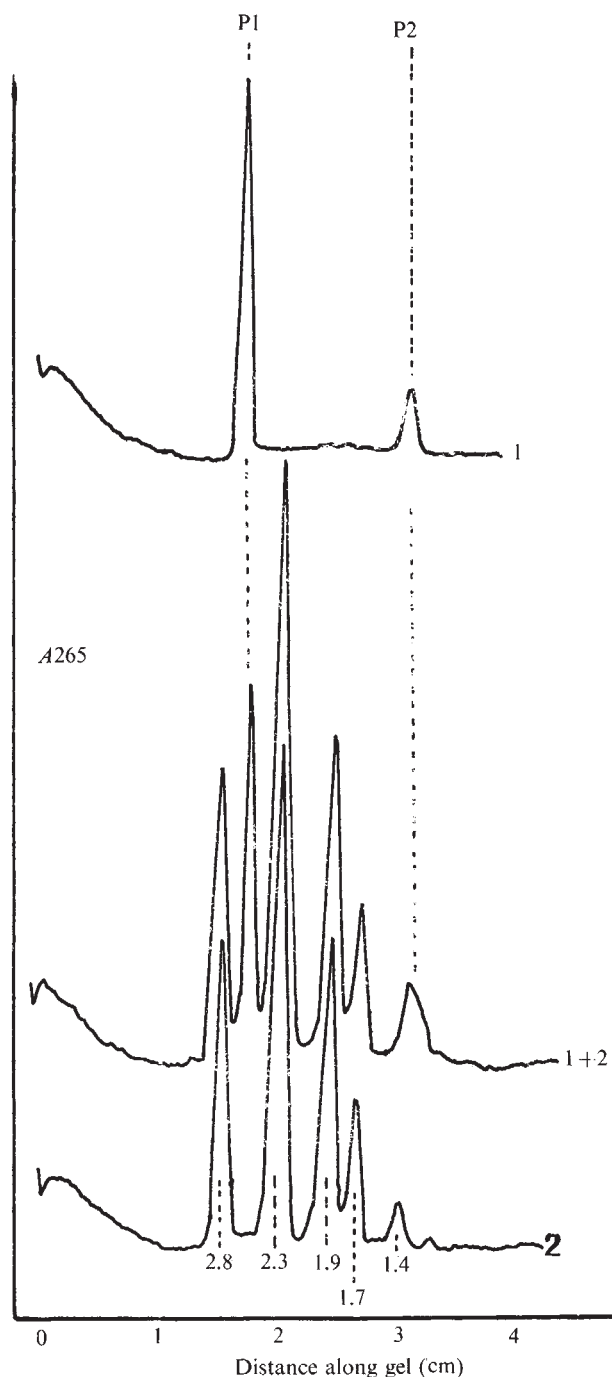


Fig. 1 Three A_{265} scans of 2.6% polyacrylamide gels prepared and run by the method of Loening²⁷. Scan 1 (top) shows a gel loaded with 1.0 μg of yeast dsRNA isolated from strain KB. Scan 2 (bottom) shows a gel loaded with 3.5 μg of a mixture of S and F *Aspergillus foetidus* virus dsRNA (the figures beneath the peaks indicate the molecular weights of each peak $\times 10^6$). The peak labelled 2.3 is a mixture of two components of molecular weight, 2.31 and 2.24 respectively, which are not resolved by gel scanning but which are just distinguished when the gel is stained. Scan 1+2 shows a gel loaded with 1.0 μg yeast dsRNA and 3.5 μg *Aspergillus* virus dsRNA. The gels were electrophoresed for 8 h at 4 mA per gel.

controlled pore size glass granules (BDH, 37 nm). The fraction running off the column at its void volume was precipitated with cold alcohol, taken up in 0.05 M Tris buffer containing 0.01 M NaCl, 0.001 M EDTA and 15% ethanol, pH 6.98, and loaded on to a column of CF11 cellulose (Whatman). Chromatography was then performed by the method described by Franklin⁹ omitting the elution with 35% ethanol as suggested by Jackson *et al.*¹¹. Yeast

dsRNA behaved on CF11 cellulose in exactly the same manner as R17 and tobacco mosaic virus dsRNA^{9,11}, eluting only when the column was washed with buffer containing no ethanol.

Analysis of the nucleic acid eluted from CF11 columns with 0% ethanol by polyacrylamide electrophoresis may be seen in scan 1 in Fig 1. The first peak on the gel, labelled P1, is equivalent to the peak X reported by Berry and Bevan¹, while the other peak, labelled P2, of higher electrophoretic mobility, is a fraction which was obscured in their experiments by the 26S rRNA and which is only present in some strains. Although strains have been found which do not possess any detectable dsRNA, most of those investigated contain either P1 alone or P1 and P2 dsRNA. No strain has yet been found to possess the P2 dsRNA only. In strains which have both P1 and P2 dsRNA, P1 always seems to be the predominant species, the amount of P2 varying between 10 and 30% of the amount of P1 as judged by the respective peak areas. Since the extraction procedures used yield single stranded RNA in an undegraded form it seems unlikely that P2 dsRNA is formed by the degradation of P1 dsRNA during the extraction procedure. Nevertheless, the possibility that P2 dsRNA represents a stable intracellular degradation product of P1 cannot be discounted.

Identical peaks of dsRNA together with a DNA peak are found when total nucleic acid preparations made after cell breakage are analysed on polyacrylamide gels after the obscuring rRNA has been removed by precipitation with 2 M Li^+ (ref. 12), or by treatment with 1.0 $\mu\text{g ml}^{-1}$ RNase A in $1\times\text{SSC}$ for 10 min.

P2 dsRNA has been identified by its nuclease resistance, which resembles that of P1 (that is, similar to peak X of Berry and Bevan¹), by its property of staining pink with toluidine blue¹ and by its behaviour on CF11 cellulose columns.

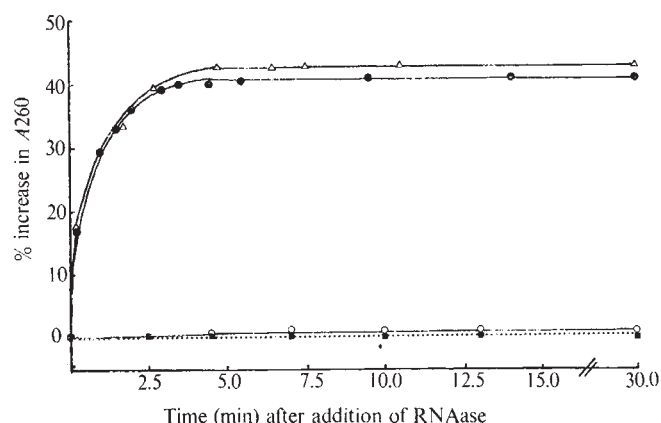


Fig. 2 The development of hypochromicity with time at 260 nm after the addition of 1.0 $\mu\text{g ml}^{-1}$ of RNase A to solutions containing 8 $\mu\text{g ml}^{-1}$ of yeast dsRNA from strain 3/A1 (peak 1 only) of different ionic strength. $\triangle$, 0.01 $\times\text{SSC}$; $\bullet$, 0.1 $\times\text{SSC}$; $\circ$, 0.01 $\times\text{SSC} + \text{Mg}^{2+}$ (10^{-2} M); $\blacksquare$, 1.0 $\times\text{SSC}$.

P1 dsRNA, which is a single molecular species as judged by its behaviour on polyacrylamide gels, has been investigated further by several techniques. The results shown in Fig. 2 demonstrate that its resistance to digestion by 1.0 $\mu\text{g ml}^{-1}$ RNase A (Sigma, crystalline grade) is entirely dependent on the ionic environment. In the absence of an appreciable salt concentration or the presence of Mg^{2+} addition of the enzyme causes a rapidly developing hypochromicity indicative of hydrolysis. The behaviour of P1 dsRNA is thus identical to that shown by reovirus dsRNA¹⁸.

Figure 3 shows the melting behaviour exhibited by P1 dsRNA in three different buffers. The sharpness of the profile once more confirms the double stranded nature of the molecule and curves *a* and *b* show that the stability of the secondary structure depends on the ionic environment as the two buffers differ only in salt concentration. Curve *c* was obtained in $1\times\text{SSC}$ (0.15 M NaCl-0.015 M Na citrate, pH 7.0) and thus allows the application of the expression given in Cox *et al.*¹⁴ relating the T_m at this salt concentration to the G+C content of the molecule. The formula suggests that the measured T_m of 99.3°C is indicative of a G+C content of 49.6%.

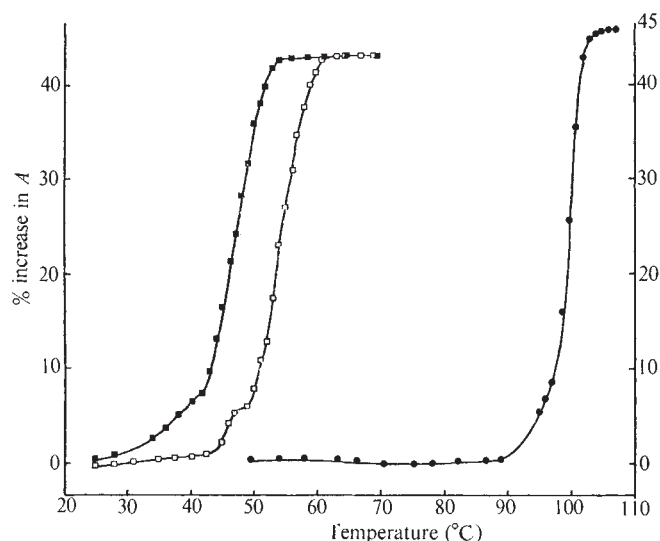


Fig. 3 Ultraviolet absorbance-temperature profiles of peak 1 dsRNA from yeast strain 3/A1 in three different solvents. ■, 0.1 SSC+67% formamide (measured at 265 nm) $T_m = 46.5^\circ\text{C}$; □, 0.5 SSC+67% formamide (measured at 265 nm) $T_m = 53.8^\circ\text{C}$; ●, 1.0 SSC (measured at 260 nm) $T_m = 99.3^\circ\text{C}$.

Two direct measurements of the base ratios of P1 dsRNA have been made using the DEAE cellulose column technique, described by Holness and Atfield¹⁵, to separate the nucleotides. In the first experiment hydrolysis was performed with T2 RNase (Sankyo) and was preceded by denaturation of the dsRNA with 85% dimethyl sulphoxide by the method described by Katz and Penman¹⁶. A sample of 100 μg of dsRNA from yeast strain 3/A1 was used for the analysis. A subsequent report by Nicolaieff *et al.*¹⁷ that dimethyl sulphoxide does not completely denature dsRNA under conditions far more extreme than those recommended by Katz and Penman¹⁶ led us to doubt whether the RNA used in the first experiment was completely accessible to enzyme digestion. The experiment was therefore repeated using 200 μg of dsRNA and an alkali digestion performed as in Holness and Atfield¹⁵. The results of these two experiments are shown in Table 1. The

Table 1 Ratios of Peak 1 dsRNA from Yeast Strain 31AC

Base	Mol fraction (%)	
	Experiment 1	Experiment 2
A	29.0	27.2
U	27.2	27.6
G	23.2	22.0
C	21.2	23.0

Experiment 1 involved an enzymatic hydrolysis and experiment 2 an alkaline hydrolysis. In both experiments a $0.5\times 80\text{ cm}$ column was used.

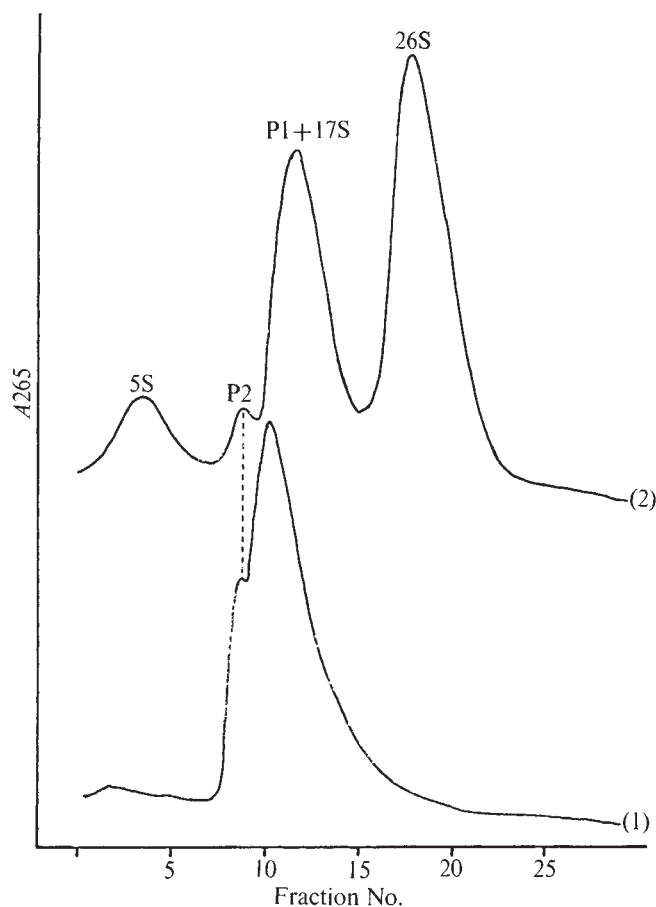


Fig. 4 Ultraviolet absorption profiles of two identical sucrose gradients produced by upward displacement of the gradients through a Uvicord ultraviolet monitor (LKB). Gradient 1 was loaded with 250 μg of yeast strain 4/4D dsRNA, gradient 2 was loaded with 50 μg of 4/4D dsRNA+320 μg of total nucleic acid from strain pS wt. The identification of the P2 and P1+17S rRNA peaks of gradient 2 was made possible by polyacrylamide gel electrophoresis analysis of the individual fractions. The gradients were spun for 19 h in a Spinco SW 25(1) rotor at 22,500 r.p.m.

equivalence of A to U and G to C once more indicates the double stranded nature of the molecule. The G+C content of the molecule is 45% and is thus lower than that suggested by the T_m . Cox *et al.*¹⁴, however, note similar discrepancies and suggest that base sequence may slightly modify the melting behaviour.

Two other findings support the identification. P1 dsRNA gave no colour in the diphenylamine assay for DNA^{18,19}. The molecule did, however, induce interferon in mouse L cells exposed at a concentration of $0.5\text{ }\mu\text{g ml}^{-1}$ (plus 25 $\mu\text{g ml}^{-1}$ DEAE dextran carrier) as judged by the subsequent resistance of the cells to infection with Semliki Forest virus.

The molecular weight of the two species of yeast dsRNA has been investigated by two approaches. First, an estimate of their $S_{w,20}$ values was made by comparing their sedimentation properties on sucrose density gradients with yeast rRNA standards. Sucrose gradients of 15–30% sucrose were used containing 0.5% sodium lauryl sulphate, 0.01 M Tris, pH 7.4, 0.001 M EDTA and 0.1 M NaCl¹⁶. Figure 4 shows the results of an experiment in which both species of dsRNA sedimenting alone were compared with a companion gradient in which both the species were co-sedimenting with yeast total RNA. P2 dsRNA is resolved as a discrete peak in both gradients and this peak was thus used to align the two optical density traces. In the gradient containing dsRNA and yeast total RNA the P1 dsRNA

is not resolved from the 17S rRNA peak; the positions of the two species on the gradient were thus found by fractionating the gradient into 1 ml fractions and examining

these fractions by polyacrylamide gel electrophoresis. The S values attributed to the two rRNA species were those found by Bruening and Bock²⁰. A value of 5S was attributed to the low molecular weight peak as formamide gel electrophoresis²¹ fractionated this class into three components which were assumed to be the 4S, 5S and 5.8S RNAs described by Uden and Warner²². The above experiment yields estimates of 15.0S for P1 dsRNA and 12.5S for P2 dsRNA, while two other similar experiments gave estimates of 15.5S and 16.0S for P1 and 13.2S for P2. Applying the relationship between the S value and molecular weight given by Franklin²³ (molecular weight, $2.24 \times S^{5.16}$) gives molecular weights of $2.6-3.1 \times 10^6$ for P1 and $1.0-1.35 \times 10^6$ for P2 dsRNA.

Similar molecular weights were obtained by polyacrylamide gel electrophoresis using dsRNA standards²⁴. These standards were dsRNAs from a mixture of "slow" and "fast" *Aspergillus foetidus* viruses, the molecular weights of which have likewise been calibrated by electrophoresis against reovirus standards by Ratti and Buck²⁵. Figure 5 shows the optical density scan of two gels in one of which the standards were electrophoresed alone and, in the other, together with P1 and P2 dsRNAs. Table 2 gives the molecular weights of the standards and the estimates of molecular weight of yeast dsRNAs given by this method for dsRNA derived from several different strains of yeast. The molecular weight of P1 dsRNA is thus 2.5×10^6 , and that of P2 1.4×10^6 .

Table 2 Molecular Weight Estimates of dsRNAs of Seven Yeast Strains

Strain	Peak 1 MW 10^6	Peak 2 MW 10^6	Phenotype
KB	2.50	1.40	Killer
4/4D	2.50	1.40	
3/A1	2.52	—	
a, ur ₃ , thr ₃ , li ₈ , arg ₆ , tr ₂ , m.	2.52	—	Sensitive
4D/13	2.50	0.66	
4D/14	2.50	0.75	
ad ₁₋₀ α	2.45	1.10	

The estimates were all made by co-electrophoresis of the purified dsRNA with *Aspergillus foetidus* virus dsRNA (as illustrated in Fig. 1) with the exception of strains 4D/13 and 4D/14 which were estimated using 4/4D dsRNA as a reference. MW, molecular weight.

The products of denaturation of the dsRNA were investigated to ascertain whether the molecule was a simple length of collinear duplex or whether it contained nicks, single stranded regions or side loops which, on denaturation, would yield single stranded RNA of lower molecular weight than expected and possibly RNA of two or more size classes. Initial attempts to analyse the products of denaturation utilized mild denaturation conditions¹ followed by aqueous polyacrylamide gel electrophoresis but the bulk of the denatured RNA in such experiments remained at the gel surface as an aggregate sensitive to RNase. This problem of aggregation was solved by the use of the non-aqueous polyacrylamide gel electrophoresis technique described by Staynov *et al.*²¹. The gels were prepared by an improved method to that described in ref. 21, communicated to us by Gratzner and Pinder (personal communication, see legend Fig. 5). Yeast P1 dsRNA ran on these gels as a single band with roughly the same mobility, relative to yeast rRNA, as is found in the aqueous polyacrylamide gel technique. Non-aqueous gels cast in formamide can be stained with toluidine blue if they are left in distilled water for 3-4 h before staining. In these conditions the dsRNA continues to stain pink while the rRNA stains blue. These findings suggest that the molecule has retained its secondary structure and agree with the report of Strauss *et al.*²⁶ that dsRNA is not denatured simply by dissolution in formamide at room temperature.

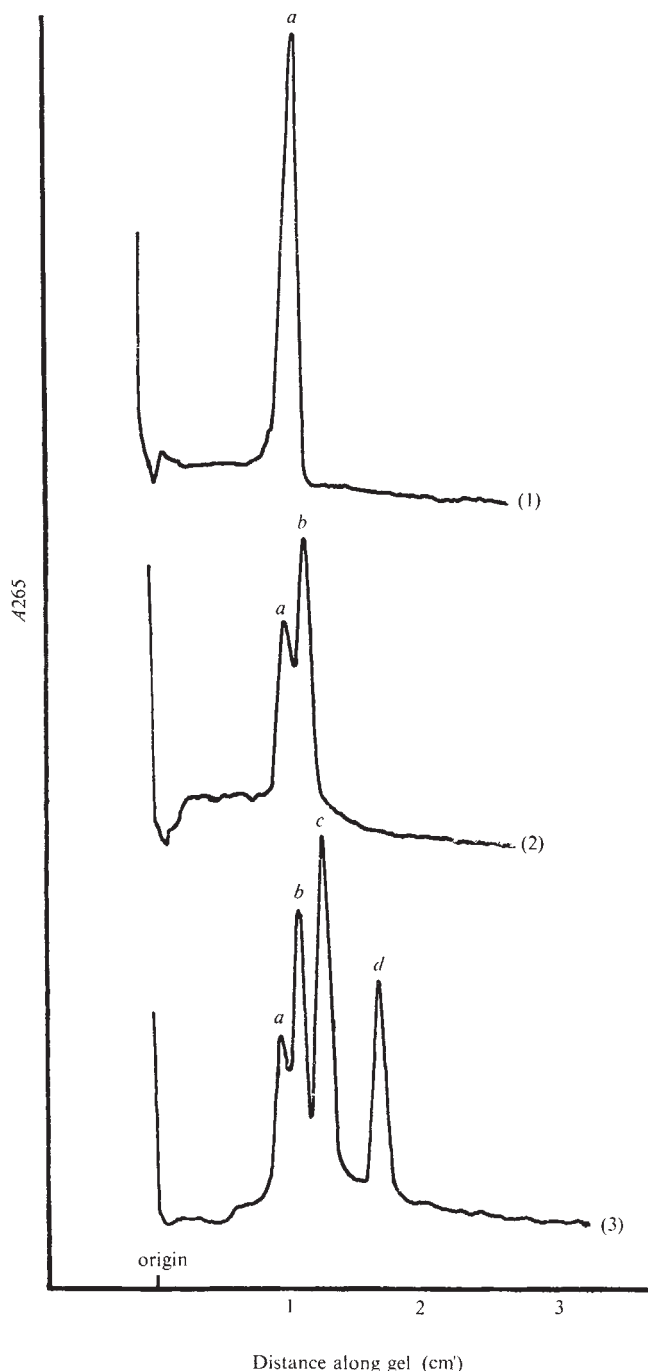


Fig. 5 Three A_{265} scans of polyacrylamide cast and electrophoresed in formamide²⁰. Scan (1) is of a gel loaded with 4 μ g of peak 1 dsRNA from yeast strain 3/A1. Scan (2) is of a gel loaded with 4 μ g of strain 3/A1 dsRNA formerly heated to 65°C for 20 min in buffered formamide plus 10% sucrose before loading. Scan (3) is of a gel loaded with 4 μ g of heat 3/A1 dsRNA plus 6 μ g of yeast total RNA from yeast strain pS wt₁. Peak a is undenatured dsRNA; peak b, denatured dsRNA; peak c, 26S rRNA, and peak d, 17S rRNA. Peaks b, c and d stained blue with toluidine blue while peak a stained pink. The gels were prepared by the method of Staynov *et al.*²¹ except that 'Amberlite' monobed resin MB-1 (BDH) was used and the formamide was buffered with 0.02 M diethyl barbituric acid. Electrophoresis was performed with the gel overlaid with 1 cm of buffered formamide and 0.02 M NaCl as an electrolyte; pH fluctuation of the electrolyte was prevented by the use of silver-KCl external electrodes. The gels were electrophoresed for 120 min at 3.3 mA per gel.

The effects of heating the dsRNA in buffered formamide plus sucrose to 65° C for 20 min just before loading the gel can be seen in Fig. 5. The pink staining band persists but is reduced, and a second blue staining band of higher mobility appears at its expense. Co-electrophoresis with yeast rRNA has shown that this blue staining band has a mobility slightly lower than that of the 26S rRNA. It is assumed that this blue staining band represents the single stranded RNA formed by heat denaturation of the dsRNA. The fact that only one band of relatively high molecular weight appears suggests that the dsRNA is a simple collinear duplex. In fact the calculated molecular weight of the single stranded RNA is higher than the 1.25×10^6 expected from the estimate of the molecular weight of the dsRNA made above, being from 1.5×10^6 to 1.8×10^6 relative to the values for yeast rRNA given by Bruening and Bock²⁰ and Staynov *et al.*²¹ respectively. This apparently high value may be due to differences in secondary structure since the formamide gel technique was not strictly non-aqueous in our hands and it has already been shown that very high formamide concentrations are necessary to completely abolish all secondary structure²⁶.

The relationship between the possession of dsRNA and the killer character was initially investigated by examining the nucleic acid of several strains of killer, neutral and sensitive phenotypes by gel electrophoresis to detect the presence of dsRNA. So far forty-nine strains have been examined (twenty-one "killers", five "neutrals" and twenty-three "sensitives") and at least as many more spore cultures from killer by sensitive and sensitive by sensitive genetic crosses. These tests have revealed that while killer and neutral strains have both P1 and P2 dsRNA, sensitive strains, with three exceptions, possess only P1 dsRNA or lack dsRNA at detectable levels. The three sensitive strains possessing both species of dsRNA are from two sources: *ad₁α* is a haploid petite strain while strains 4D/13 and 4D/14 are both diploid and were isolated as spontaneously occurring sensitives from a killer diploid. In both cases the P2 dsRNA isolated from these strains has a lower molecular weight, as judged by polyacrylamide gel electrophoresis, than that isolated from the two killer strains analysed (see Table 2) and co-electrophoresis of a mixture of dsRNAs from these killers and the sensitive dsRNA from these strains reveals two distinct P2 bands. Although several of the yeast strains tested probably have a common ancestor and differ only in nutritional requirements, it should be noted that the twenty-three killer strains analysed do include strains from two other laboratories and also include four naturally occurring killer strains isolated as brewery contaminants.

The finding of this correlation led naturally to a series of experiments in which killer and sensitive strains were crossed and the phenotype of the progeny (and parents) with regard to the killer character and possession of the two peaks was determined. The results of these crosses will be reported in detail elsewhere. They show that both peaks of dsRNA (symbolized as a ++ phenotype) are present only in strains possessing the nuclear allele *M*^{3,4,28}. Strains with the recessive allele *m* either lack both peaks (— phenotype) or only possess the first peak (+—). The following types of strain have been identified by biochemical analyses of the dsRNA phenotypes associated with particular genotypes as deduced from breeding experiments: *m*(—), *m*(+—), *M*(—), *M*(+—), and *M*(++). Only the last of these strains yields the killer toxin^{3,6} and has the killer phenotype; the rest are sensitive to the toxin. When both fractions of dsRNA are present in killer cells they seem to be inherited together and cannot be separated from one another by appropriate genetic crosses. For example, the diploid derived from the cross *M*(++) killer × *m*(—) sensitive yields tetrads of spores in a ratio of 2 *M*(++) killer:2 *m*(—) sensitive. No *m*(+—) spores are recovered from this cross as would be expected should

the first and second fraction of dsRNA be separately located in the cell, that is $(++) = (+_1)(+_2)$. On the other hand, *m*(+—) spores are recovered wherever one parent of a genetic cross is *m*(+—). It is interesting that the recovery of *m*(+—) spores following a *m*(+—) × *M*(++) cross indicates that a *Mm*(++) (+—) diploid is formed, although, unfortunately, this cannot at present be demonstrated biochemically.

These genetic studies suggest that the (++) and (+—) phenotypes have separate particulate bases: the former can only be maintained in the presence of the *M* nuclear allele whereas the latter can be maintained by either *M* or *m*.

Although the dsRNA fractions have been referred to as phenotypes, it will be appreciated that the occurrence of *M*(—) and *m*(—) strains indicates that at least the first of these fractions itself possesses genetic continuity in the sense that once lost it cannot arise *de novo*. In genetic terminology the dsRNA fractions described can be referred to as cytoplasmic determinants whose maintenance is governed by the nuclear gene *M/m*. Previous publications^{4,5} have referred to killer genotypes as *M*(k) and sensitives as *M*(o) or *m*(o), (k) and (o) symbolizing respectively the presence and absence of killer cytoplasmic genetic determinants. We can now redefine these genotypes in terms of the presence or absence of dsRNA peak 1 and 2 fractions and, in so doing, go a step further and differentiate between (+—) and (—) sensitive strains.

In view of the results reported here we have used techniques different from those adopted so far to establish whether or not virus-like particles similar to those described in *Penicillium* and *Aspergillus* are associated with our strains. Using the methods of Charney *et al.*²⁸ as modified by Ratti and Buck²⁵ we have been able to show that such particles are present in post-mitochondrial supernatant fractions of killer (++) and sensitive (+—) strains but absent in sensitive (—) strains. These virus like particles are similar in appearance and within the same size range as those fungal viruses described by other workers²⁹⁻³², possessing an average diameter of 39.2 nm. Present studies are directed at establishing a relationship between these particles and the peak 1 and 2 dsRNA fractions.

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LETTERS TO NATURE

PHYSICAL SCIENCES

Low Frequency Radio Emission from Extensive Air Showers

RADIO pulses associated with extensive air showers have been observed over a frequency range of 2 MHz (refs 1 and 2) to 550 MHz (ref 3). Up to now measurements over the range of 20 MHz to 100 MHz have proved to be those most easily made⁴. At the highest frequencies a decrease in the lateral extent of the radiation, a decrease in its amplitude and increasing receiver noise have limited observations. At the lowest frequencies the overriding experimental problem is background noise. Only the use of highly directional antennas² or the reduction in daytime noise due to ionospheric D-layer absorption¹ have enabled measurements to be made down to 2 MHz. But the lowest frequencies hold particular interest since the large amplitudes reported seem to be in gross disagreement with theory⁵. Also, long wavelength radiation might prove to have a large lateral spread which could be exploited in the form of a large air shower detecting array.

Except in the most remote areas, the frequencies immediately below 2 MHz are not useful because of the presence of broadcasting. Below the medium wave broadcast band, however, there is a range of frequencies which, in Australia at least, is still relatively unused. Here we report preliminary work in this region.

The receiver had a bandwidth of 80 kHz centred on 100 kHz. There was no detector stage and the amplified radiofrequency signal was observed directly. The antenna consisted of a length of copper wire, 98 m long, suspended about 3 m above ground. This fed 50 Ω coaxial cable. The amplified signal was recorded by a digital transient recorder. This device continually samples and digitizes an input waveform to six-bit accuracy, storing the measurements in a 256-word shift register. On receipt of a trigger signal sampling is stopped and the stored information (representing the previous 256 samples) is then available for output. By judicious choice of trigger delay it is possible to ensure that the time of interest is at any preferred part of the memory. Digital to analog conversion of the stored data allows graphical representation of the recorded signal on a chart recorder (Fig. 1). We used a sampling interval of 1 μ s, corresponding to a total cycle time of 256 μ s, although the recorder displays only 224 μ s of this on the chart trace. This sampling interval allows satisfactory reconstruction of a sampled 100 kHz signal. A trigger indicating the arrival of an air shower was derived from the fast timing part of the Adelaide University air shower array at Buckland Park. This

consists of five scintillators in a square array of side 31 m with a 1 m² scintillator at each corner and at the centre. A coincidence, with a resolving time of 150 ns, between the centre scintillator and any three of the remaining four was used to produce the air shower trigger. A mean shower rate of one per 500 s was used, corresponding to primary energies of about 10¹⁵ to 10¹⁶ eV.

Measurements have been made in a routine way since March 1973 and some 10,000 showers have been recorded. Background noise at 100 kHz has considerable variability, particularly from day to night. Traces were rejected if their maximum excursions were greater than a predetermined level outside the region where an EAS pulse might be expected: about 2% of all events were rejected on this basis. The remaining traces were then integrated by sampling at three points: where the pulse would be expected and at fixed but arbitrary times before and after the pulse region. In each case the largest peak-to-peak amplitude in a 30 μ s interval was recorded. The measured outputs were squared then added so that two summed squared noise measurements and a summed squared signal-

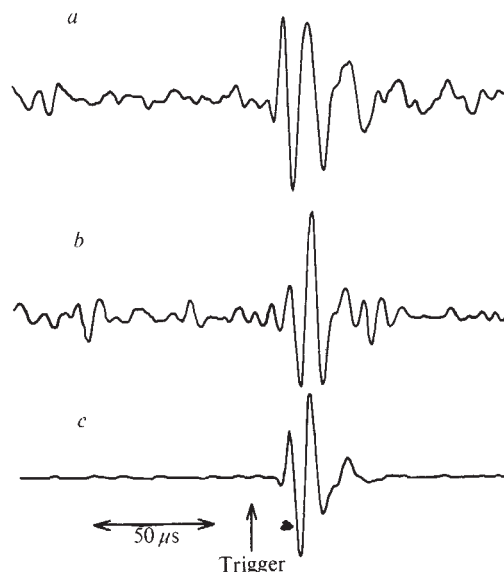


Fig. 1 *a* and *b*, Tracings of recorded receiver outputs showing typical 100 kHz radio pulses. The signal was sampled every microsecond. *c*, Similar recording of the impulse response of the receiver (input pulse rise time 20 ns, fall time 50 ns). The input pulse was applied at the time indicated by "Trigger".

plus-noise measurement were obtained. Subtraction of summed squared noise from summed squared signal-plus-noise enabled the r.m.s. signal and r.m.s. noise level to be extracted. This sampling technique has been investigated by J. H. Hough and J. R. Prescott (private communication) and shown to produce satisfactory retrieval of signal from noise. The mean r.m.s. signal-to-noise ratio obtained was about two, although for reasons discussed below this can only be used as a guide. Many individual pulses are clearly visible above the noise.

Because it is possible for electronic recording equipment to pick up spurious signals, we have triggered our air shower array and radio receiving system with artificially generated signals in an attempt to produce pickup. We have been unable to produce any significant amount of spurious signal which would be confused with genuine signals. The real signals that have been observed usually have such a large signal-to-noise ratio that it is most unlikely that there has been any significant contamination of the observation with spurious signals. We note, without entering into details, that there is a positive correlation between pulse amplitude and shower size, an observation unlikely to be compatible with spurious signals. Typical large signals are shown in Fig. 1, with the impulse response of the amplifier.

The antenna described above has provided the best signal to noise ratio we have observed so far; however, its properties are not amenable to a simple calculation. For this reason a 9 m long vertical "whip" antenna has also been used with a receiving system similar to that described above and both systems operated simultaneously. The whip antenna has properties which are readily calculated (ref. 6, page 400). From such a calculation and intercomparison of the results from the two antennas it was concluded that the r.m.s. vertical field strength of the observed pulses was about $500 \mu\text{V m}^{-1} \text{MHz}^{-1}$. Background noise measurements gave results consistent with published predictions (ref. 6, p. 481).

Published results at 22 MHz (ref. 8), 6 MHz (ref. 7) and 2 MHz (ref. 2) together with the present results (normalized, following convention, to showers of 10^{17} eV primary energy and assuming a geomagnetic emission mechanism) define a spectrum of field strength ϵ against frequency ν which can be represented as a power law, $\epsilon(\nu) \sim \nu^{-1.5}$. If we assume that the radio signal extends over an area $\sim \lambda^2$, then an estimate of the total energy E radiated at frequencies greater than some lower limit ν_0 gives $E \sim 10^{14} \nu_0^{-4}$ J (with ν_0 in Hz). A cutoff frequency of 20 kHz would result in the energy radiated being equal to the total primary energy. This suggests that an additional energy source is needed.

We have observed a substantial variation in the r.m.s. signal amplitude with time, the time variation being on a scale of days together with a smaller diurnal variation. On occasions the signal has remained at r.m.s. amplitudes at least twice as large as the mean quoted above for some days, but on one occasion at least it fell to less than 10% of the r.m.s. noise level for almost two days. Further, as shown in Fig. 1, observed pulse shapes do not correspond closely to the impulse response of the receiver and a variety of pulse shapes has been observed. These observations are not consistent with any present theory of radio pulse emission⁴. The only mechanism we are aware of which could conceivably explain our results is that in which the observed signal arises from an interaction between the vertical electric potential gradient existing in the atmosphere and the ionization due to the air showers. Various aspects of such a mechanism have been discussed previously^{9,10}. Wilson⁹ concludes that shower-induced changes in the local atmospheric potential gradient with time scales greater than 1 μs should be observable, whereas Charman¹⁰ suggests that at 10 MHz the field strength should be comparable with that due to other mechanisms considered.

In conclusion, radio pulses with a large signal-to-noise ratio have been detected in coincidence with extensive air showers using a 100 kHz receiver of 80 kHz bandwidth. The nature of this phenomenon appears to be different from that at frequen-

cies above 20 MHz. This may well lead to a resolution of the discrepancy⁵ between theory and experiment at low frequencies and may possibly be related to the existence of a non-geomagnetic component in high frequency work⁸.

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Atmospheric Gravity Wave Observations after the Solar Eclipse of June 30, 1973

It has been suggested that, during a solar eclipse, gravity waves are generated by the Moon's shadow moving with supersonic speed through the Earth's atmosphere^{1,2}. After the eclipse of March 7, 1970, several investigators³⁻⁶ detected atmospheric gravity waves in the form of travelling ionospheric disturbances (TIDs) using different observational techniques. But it was not possible to decide definitely whether the TIDs were due to the eclipse or to any other sources.

The solar eclipse which occurred on June 30, 1973, between 0900 and 1415 UT over the North Atlantic and Africa, provided another opportunity to identify eclipse-generated gravity waves. Beer and May⁷ and Frost and Clark⁸ performed ray tracing calculations and predicted positions and times at which, as a consequence of the curved eclipse path, focusing of the waves should occur. The principal focus of the southward-propagating waves is over South West Africa on the edge of the penumbra, where the wave amplitude at ionospheric heights should be five to ten times greater than the predicted amplitude in the focusing area over California after the eclipse in 1970. The onset of the eclipse-induced waves over South West Africa was expected after 1415 UT.

The field station Tsumeb (19° 14' S, 17° 43' E), which is operated by the Max-Planck-Institut für Aeronomie, lies near the predicted focus of the south-going waves. On June 30, 1973, four experiments were carried out during and after the eclipse. (1) Vertical incidence ionograms were taken every 5 min. (2) The Faraday rotation angle of the 137 MHz signal of the geostationary satellite Intelsat II F3 (elevation angle $\approx 45^\circ$, azimuth $\approx 60^\circ$ west of north) was recorded at Tsumeb and two additional stations, Outjo (20° 07' S, 16° 09' E) and Okahandja (21° 59' S, 16° 55' E). (3) F-region TIDs were observed at horizontal distances between 900 and 1,700 km north of Tsumeb by means of h.f. ground-backscatter ionograms taken every 4 min. (4) A microbarograph recorded ground pressure variations. Figure 1 shows the results of the F-region measurements between 1000 and 2000 UT. Unfortunately, the observations seem to be affected by a geomagnetic storm which

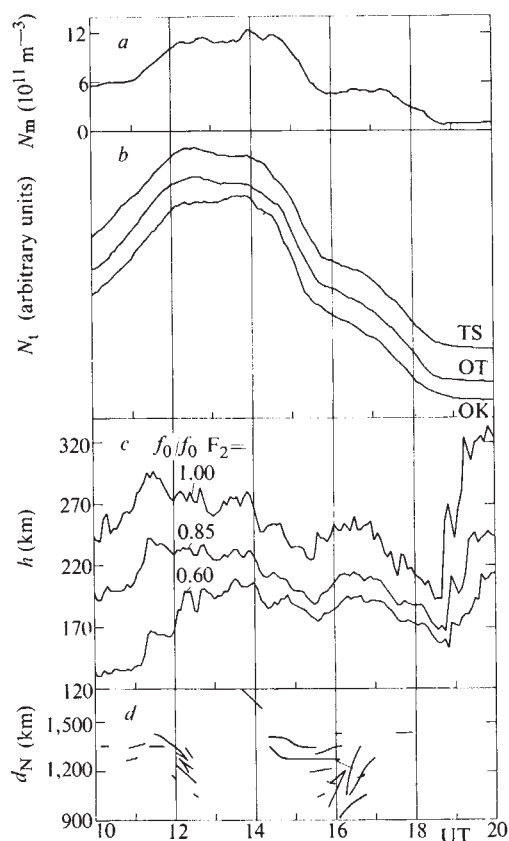


Fig. 1 Ionosphere observations during and after the solar eclipse of June 30, 1973. (a) Electron density at the F-layer maximum; (b) total electron content at Tsumeb, Outjo and Okahandja; (c) real heights of normalized ionization levels; (d) horizontal distance between Tsumeb and TIDs occurring north of Tsumeb.

started at 2230 UT on June 28, 1973, and had K_p values up to 6+ during the following day.

Figure 1a shows the electron density at the F-layer maximum, N_m , which was deduced from the vertical incidence ionograms. From 1000 to 1100 UT and from 1600 to 2000 UT, the variation of N_m exhibits a regular and undisturbed behaviour. Between 1100 and 1600 UT, however, a large disturbance occurs which enhances N_m by a factor of 2. It is most probably caused by changes in the thermospheric wind system and composition which, on their part, are due to the geomagnetic storm⁹. Between 1330 and 1500 UT a wave-like disturbance with a relatively small amplitude of about 5% can be seen.

Figure 1b shows the total electron content N_t which was derived from the Faraday measurements at Tsumeb (TS), Outjo (OT) and Okahandja (OK). The ordinates for the three curves are displaced relative to each other. The maximum electron content, like N_m , is much greater than during geomagnetically quiet days. After 1300 UT, a small disturbance was observed at Okahandja. Because the Faraday measurements at Okahandja are mainly determined by the ionosphere at roughly the latitude of Tsumeb, this disturbance is probably identical with the simultaneously observed wave-like disturbance in N_m . But it does not appear in the N_t curves of Tsumeb and Outjo, and is consequently a localized phenomenon without any connexion to the eclipse.

Figure 1c shows the real heights h of three normalized ionization levels $f_0/f_0 F_2 = \text{const}$ (f_0 = plasma frequency, $f_0 F_2$ = critical frequency of the F₂-layer), which were calculated from the vertical incidence ionograms¹⁰. The level $f_0/f_0 F_2 = 1.00$ is the height of the F-layer maximum. The height change between 1030 and 1530 UT corresponds to the large disturbance in N_m and is due to the geomagnetic storm. It seems to be superposed by a few oscillations of small amplitude

which are associated with the wave-like disturbance in N_m between 1330 and 1500 UT. Between 1530 and 1830 UT, another quasisinusoidal disturbance is recognized, the onset of which cannot, however, be determined. The relative minimum near 1530 UT appears in Fig. 1b as a point of minimum curvature in the N_t curves which occurs at Okahandja earlier than at Tsumeb and Outjo. The disturbance thus travels northwards. The rapid increase of h after 1830 UT is due to the sunset. The fluctuations superposed on the increase must probably be attributed to the reduced quality of the ionograms.

From the backscatter ionograms, the horizontal distance d_N between Tsumeb and TIDs occurring north of Tsumeb was derived (Fig. 1d). Near 1200 UT, several southward-travelling disturbances were observed which, at this time of day, were also found regularly on days before and after the eclipse. Moreover, the relatively low speeds do not allow us to attribute them to the eclipse. Another TID appeared near 1400 UT at $d_N \approx 1,600$ km moving southwards with a speed of 250 km h^{-1} . On other days of observation, no TID was found around 1400 UT; the low speed, however, again excludes any speculation about an eclipse-related origin. After 1500 UT, only northward-travelling disturbances were observed.

Between 1000 and 2000 UT, the microbarograph recorded only one oscillation train with a period of about 15 min. It started at 1315 UT, so that it cannot be caused by an eclipse-induced gravity wave.

We conclude that no eclipse-generated atmospheric gravity waves could be detected near the predicted focusing area over South West Africa.

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Was the Tungus Event due to a Black Hole?

THERE have been many attempts to explain the Tunguska meteorite, ranging from the prosaic to the bizarre¹⁻³. We suggest that a black hole of substellar mass such as those that have been postulated by Hawking⁴ could explain many of the mysteries associated with the event.

The Tunguska meteorite left a visible fiery trail accompanied by thermal radiation and a blast wave that levelled forest over several hundred square kilometres¹. No crater and no meteoritic material that can unambiguously be associated with the event have ever been found. It has been estimated that 10^{22} to 10^{24} erg (equivalent to a 0.2 to 20 Mton nuclear explosion) would be needed to destroy forest over such a wide area¹⁻³.

How can a small black hole explain the event? We assume that the black hole had the mass of a large asteroid, 10^{20} to 10^{22} g (2×10^{-8} to $2 \times 10^{-6} M_\oplus$). The geometrical radius of such an object is measured in Angstroms, but its Newtonian gravitational field can be quite strong for some distance from the body. We also assume that the velocity of the black hole

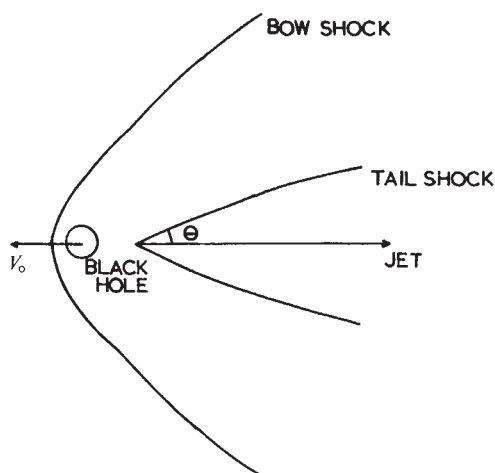


Fig. 1 Observational parameters for black hole-atmosphere interaction (see text).

was slightly greater than Earth escape velocity. An object with negligible geometrical radius will set up a shock wave such as that shown in Fig. 1 (refs. 5-7). The rate of energy deposition into the shock will be⁵

$$dE/dt = \pi \rho_0 V_0^3 C_A R_A^2$$

where $R_A = 2GM_{bh}/V_0^2$ is the "accretion radius"⁶ (M_{bh} is the mass of the black hole), V_0 the velocity, ρ_0 the density of the air, and $C_A = (S_{max}/S_{min})$. We take S_{max} to be the activity sphere of an object at the surface of the Earth, $S_{max} = [M_{bh}/M_\oplus]^{2/5} R_\oplus$, and S_{min} is the Schwarzschild capture cross section⁸, $4GM_{bh}/V_0^2$.

If the black hole begins in interstellar space with zero velocity and falls freely to the Earth's orbit its velocity relative to the Earth would be between 10^6 and 10^7 cm s⁻¹. It would traverse the last 30 km of the atmosphere in about 1 s and the total energy in the blast wave would be 10^{22} to 10^{24} erg for masses in the range 10^{20} to 10^{22} g.

The temperature in the shock wave T_s would be $10^{-1} m_A V_0^2/k$ where m_A is the average mass of atoms in the medium and k is Boltzmann's constant^{5,9}. In our case T_s is between 10^4 and 10^5 K. A blackbody spectrum at this temperature peaks between 300 and 3000 Å, so most of the radiation from the shock front would be in the vacuum ultraviolet and would be absorbed and reradiated at longer wavelengths. There would be little hard X radiation and the accompanying plasma column would appear deep blue.

These results agree well with eyewitness reports of the event¹ and with measurements of the pattern of throwdown of trees at the site¹⁰. Eyewitness reports of flash burning², descriptions of the object as a bright blue "tube"^{1,2}, and searing of trees at the site indicate a temperature compatible with T_s . Zotkin and Tsikulin¹⁰ have reproduced the throwdown pattern in a scale model tree field by means of an explosion travelling down a wire inclined at 30° to the surface followed by a static explosion some distance above the surface. Their data show that the pattern could also be reproduced by a cylindrical explosion of finite length travelling at the same angle of inclination to the surface. If the angle θ in Fig. 1 is small enough the shock wave from the black hole would resemble the shock wave from this sort of explosion.

Since the black hole would leave no crater or material residue, it explains the mystery of the Tungus event. It would enter the Earth, and the rigidity of rock would allow no underground shock wave. Because of its high velocity and because it loses only a small fraction of its energy in passing through the Earth, the black hole should very nearly follow a straight line through the Earth, entering at 30° to the horizon and leaving through the North Atlantic in the region 40°-50° N,

30°-40° W. This exit provides a check for the whole hypothesis. At the exit point there would be another air shock wave and an underwater shock wave and disturbance of the sea surface. Microbarograph records could be checked for an event similar to that caused by the entry shock¹¹ displaced by the proper amount of time. Oceanographic and shipping records could be studied to see if any surface or underwater disturbances were observed.

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Possible Syneresis Origin of Valleys on the Floor of Lake Superior

RELIEF features occur on the floor of Lake Superior in distinct zones which are related to bottom type and water depth¹ (Fig. 1). Zone A occurs in sand and gravel deposits to about 54 m depth. Deeper, the generalized sequence of sediments is bedrock, glacial till and sand deposits, red clay, red varved clay, and brown clay²⁻⁴. In zone B, a network of intersecting linear grooves of width 5 to 75 m having relief of 2 to 5 m and lengths of greater than 2 km occur in a till and red clay bottom at about 54 to 165 m depth. The grooves were probably formed by scouring by icebergs during an earlier lake stage when the continental ice sheet formed a border of the lake. In zone C, below about 165 m, the bottom consists of lacustrine clays, and a series of narrow, V-shaped valleys occur extensively on echograms¹. In this study, the valleys were examined by side-scan sonar, high resolution sub-bottom profiling, echosounding, and bottom sampling (Fig. 1).

The valleys cut through the strata of the first sub-bottom layer, sometimes reaching the depth of the next major sub-bottom reflector (Fig. 2). Separations between valleys vary from 20 to 1,100 m and the distribution is shown in Fig. 3a. The apparent depths of the valleys (Fig. 3b) vary from 0.3 to 10 m. These represent minimum depths because the bottom trace of an echogram generally represents the nearest reflector within the insonified area of the bottom. The location, depth or distribution of the valleys does not seem to be related to bottom gradient or water depth. The thickness of the sedimentary layer in which the valleys occur seems to be an important factor. Fig. 3 shows that as the layer increases in thickness, the separations and apparent depths increase and their distribution functions tend to spread out.

To study the spatial pattern of the valleys, tracks of 30 kHz, 48 kHz, and 200 kHz side-scan sonar were taken

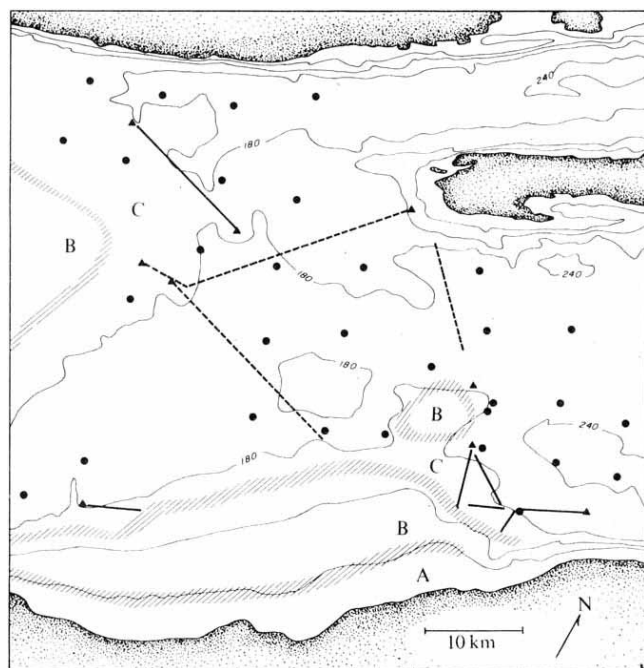


Fig. 1 Lake Superior area of investigation. —, Side-scan sonar and vertical echosounding profile; ---, sub-bottom profile; ●, Carnegie core; ▲, bottom sample. A, B and C, Physiographic zones of Berkson and Clay¹. Contour interval 60 m.

(Fig. 1). Simultaneous 25 kHz echograms indicate that slopes of the valleys facing the transducer are the principal scattering features. Sonographs display a polygonal network of connected valleys with three-valley junctions (Fig. 4a), a polygonal network with fewer or obscured connexions (Fig. 4b), and a series of isolated depressions (Fig. 4c). In some cases, sound backscattered by valleys is below the sensitivity of the sonar, and the valleyed bottom shown on the echogram is an even texture on the simultaneous sonograph. This is probably due to the extreme transparency and local smoothness of the bottom¹. The data suggest that polygonal networks occur in areas where the sedimentary layers are thinner.

The cross-sectional structure indicates that the valleys were formed after deposition of the finer sub-bottom layering. The pattern and cross section seem to preclude ice scouring and faulting as origins. Slumping is unlikely because the features are not localized or related to bottom slope. Valleys in the clay floor of the Scotian shelf having a similar echogram cross section and appearing on sonographs as crater-like depressions of diameter 15 to 400 m and apparent depth 5 to 20 m were attributed to an erosional process in which gas or water ascended from the underlying bedrock into the clays, which were then put into suspension and removed by bottom currents⁵. This process does not seem to explain the pattern and cross section of the Lake Superior valleys. The features may have been caused by some type of bottom erosion. The principal problem with erosional agents is in accounting for the pattern. We will not discuss such agents in detail here, but we will describe an alternative origin.

The structure and pattern of the valleys and their relationship to sedimentary layer thickness are characteristic of features formed in a layer of material that has undergone contraction. The history of Lake Superior^{2,3} seems to rule out subaerial drying, thermal contraction and beach/shallow water processes as origins. Subaqueous shrinkage

features on a smaller scale have been observed. Fine-grained particles in a water mixture form a mud system which may exhibit syneresis, thixotropy and other colloidal processes⁶. During syneresis, water is expelled during the gelling of the colloidal system⁷, resulting in features associated with the expulsion process and the resulting shrinkage of the sedimentary layer such as syneresis cracks, polygons, cones, and pits^{8,9}. Subaqueous features due to syneresis have been observed in laboratory experiments⁸⁻¹⁰ and small scale features observed in ancient consolidated sediments have been attributed to syneresis^{8,9,11}. Since layer thickness is a critical factor in the scale and pattern of syneresis features⁸ and subaerial shrinkage features¹², syneresis features as large or much larger than the Lake Superior valleys might occur in sediments. Large scale subaerial desiccation polygons have been reported¹³, but we are not aware of large scale submarine features attributed to syneresis. This origin accounts for the widespread occurrence, morphology, and layer thickness relationship of the Lake Superior valleys. Syneresis is likely to occur in zone C since the clays are characterized by high water content¹⁴ (Fig. 5) and very fine-grained particles, with the grey clay averaging 85% finer than 1 μ m and the grey varved clay 92% finer than 1 μ m (ref. 3). The apparent widths of the valleys range from about 3 to

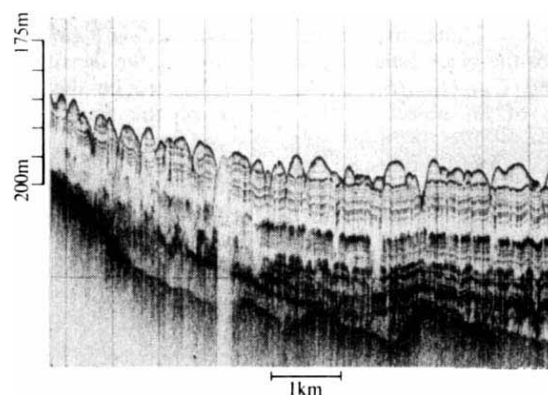


Fig. 2 Sub-bottom profile of valleys.

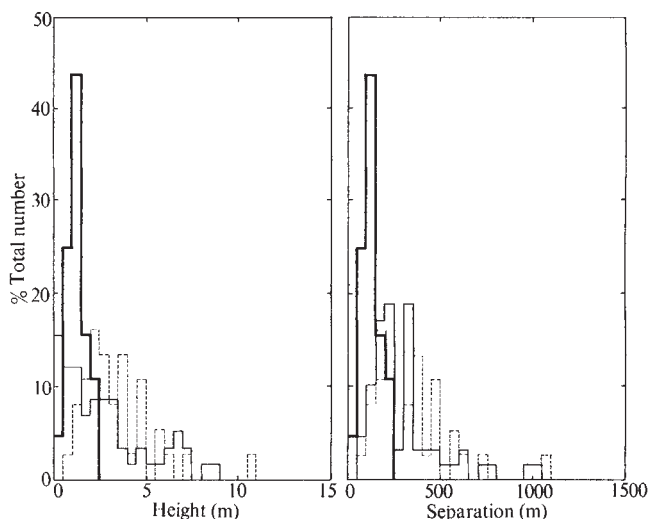


Fig. 3 Separation and apparent depth of valleys. Thickness of first sub-bottom layer: —, 6.2 m; ---, 11.4 m; ..., 14.5 m.

30 times the apparent depths, with the slope of the central part unknown. The steep slopes observed in experimental syneresis cracks might not be formed or preserved in zone C clays.

There may be a family of syneresis features of various sizes occurring in fine-grained sediments of the ocean and lake floors. Based on experiments⁸⁻¹⁰, important factors in determining the character of the features might be sediment type, electrolyte type and concentration (such as salinity), and layer thickness. Other factors might be sedimentation rate, character of the underlying layer, and bottom slope. Earthquakes might have an effect by causing liquefaction of the sediments by thixotropy¹⁵ or by speeding the expulsion of water. Syneresis might be considered as an alternative hypothesis for the Scotian pockmarks⁵, Lake Michigan pockmarks (J. M. B. Gross,

and Lineback, unpublished), depressions on the Mediterranean continental slope attributed to slumping¹⁶, features observed in sediments after the Alaska earthquake¹⁷, or features observed on bottom photographs attributed to degassing of sediment¹⁸, lebensspuren¹⁹, and so on. But the very small features may be short lived because of erasure by small-scale biogenic activity²⁰ or by many superimposed lebensspuren. Further studies of the mass properties of the bottom and additional experiments will be helpful in evaluating this origin.

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Climate and the Galapagos Islands

COLINVAUX¹ has suggested that the Galapagos Islands were dry during the period from about 30,000 to 10,000 BP and that this was because the intertropical convergence zone (ITCZ), which at present brings rain to the area in the early part of each year, remained north of the geographical equator during this period. Here I shall examine the obvious alternative possibility, namely that the ITCZ remained south of the geographical equator during the period.

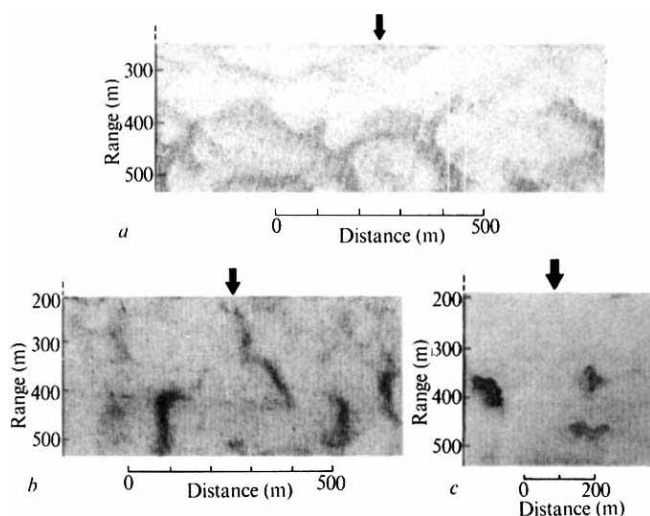


Fig. 4 Sonographs of valleys.

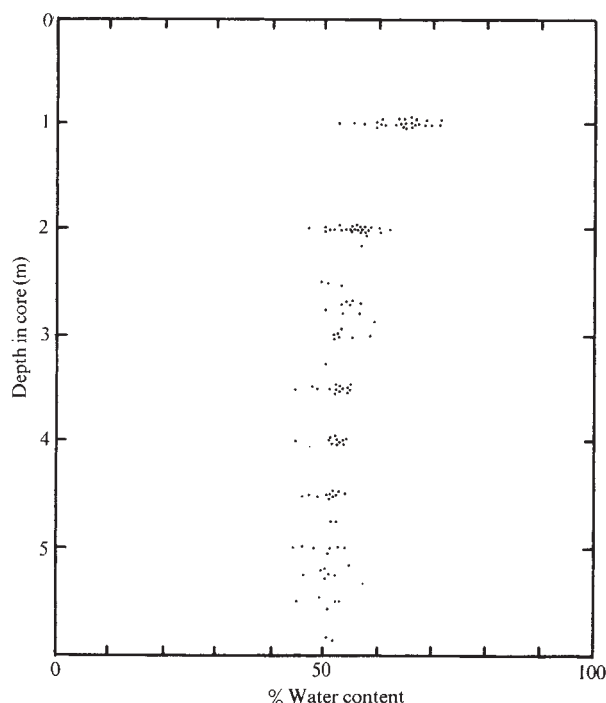


Fig. 5 Water content of clay floor. % Wet weight of Carnegie cores shown in Fig. 1.

Although it may be premature to state that there is a satisfactory theory to explain the latitude of the ITCZ and its variation with longitude and season, there are now available extensive observations of the variation which can be found in standard textbooks of climatology for land areas² and obtained from satellite cloud photographs for the ocean areas³. One can also use mean wind observations in the free atmosphere to compute the field of rising motion⁴, and this has been done both for the zonal mean and as a function of longitude.

It is possible to view the mean Hadley cell meridional circulation as driven by the middle latitude baroclinic eddy processes which are themselves linked to the temperature gradients across middle latitudes^{5,6}. In Table 1 is shown the temperature difference between latitudes of 70° and 20° for both hemispheres for four seasons at a level of 700 mbar together with the latitude of the centre of the mean rising motion⁴. (Note that when the temperature gradient across middle latitudes increases, the ITCZ moves away from the maximum gradient.) In January with the largest gradient in the northern hemisphere, the mean position is south of the equator. As the southern hemisphere gradient outweighs the northern hemisphere gradient in June–August, so the mean position moves to the north of the equator. The mean position over the four seasons is to the north of the equator while the mean gradient is greatest in the southern hemisphere. In addition, the sum of the gradients in the two hemispheres, which may be regarded as the overall forcing function for the intensity of the Hadley cell circulation, is a maximum in December–February and it has been argued previously that the Hadley cell intensity is also a maximum then as evidenced by the occurrence of the lowest annual temperatures at the tropical tropopause⁷.

Table 1 Middle Latitude Temperature Gradient at 700 mbar and Mean Position of Rising Motion

	20–70° N	20–70° S	ITCZ latitude	Gradient sum
December–February	31	27	6S	58
March–May	28	29	1S	57
June–August	15	31	7N	46
September–November	25	30	6N	55
Mean	25	29	1.5N	54
Estimate for 20,000 BP	40	37.5	? S	77.5

From data in ref. 4. Units: °C.

Turning to 20,000 BP, where mean temperatures are only available for the precipitation season at high latitudes, it can be seen from ice core data⁸ on $\delta(^{18}\text{O}/^{16}\text{O})$ that the temperature gradient in the northern hemisphere increased more than that in the southern hemisphere. If the isotope ratio data are converted to equivalent temperature changes, using present day variation in temperature and ratio as a guide, it is found that temperatures at 77° N were lower in 20,000 BP than now by about 20° C while those at 80° S were only decreased by about 13.5° C. It is therefore possible that the temperature gradient in the northern hemisphere exceeded that in the southern hemisphere with the implication from Table 1 that the mean position of the ITCZ would be south of the geographic equator.

Of course this does not imply that at the specific longitude of the Galapagos Islands the position was to the south. The latitudinal displacement of the ITCZ depends markedly on longitude, being larger over eastern South America and Eastern Africa and the Indian Ocean region than over the Central and Eastern Pacific and the Atlantic. Additional evidence for the present hypothesis is therefore best sought in regions where the present displacement is small. Presumably the Peruvian desert coast must have been wetter than now;

there is some evidence of a considerable accumulation of ice in North-west Peru during the last glaciation⁹. On the other hand on the eastern side of the continent near Georgetown, Guinea, where a larger latitudinal displacement might be expected there is evidence of dryer conditions¹⁰. There is also some evidence that the Amazonian forest was drier than at present¹¹.

On the west coast of Africa where now the mean ITCZ position is north of the equator there is evidence that towards the end of the last glacial period conditions were much drier and in fact it is thought that dunes invaded the savanna across a broad belt from the Atlantic coast to the Nile Valley¹². This could be interpreted as a southward shift in the mean position of the ITCZ. Again conditions varied with longitude and in fact before 21,000 BP Lake Chad was much more extensive than at present¹²; however, it is difficult to decide whether this was due to greater rainfall or lower temperature.

In Table 1 it is assumed that temperatures at 20° N and 20° S were 5° C lower in 20,000 BP than now. Notice that the gradient sum which I argued earlier gives a measure of the Hadley cell intensity is also greater for 20,000 BP. It is hard to relate intensity and sum for a previous period because a smaller moisture content was presumably associated with the lower temperature and the latent heat forcing which plays such a large role in the atmospheric energy cycle may therefore have been lower.

Finally it is desirable to obtain a clearcut physical linkage between the middle latitude temperature gradients and the position of the ITCZ. One such chain of events has been described by Namias¹³ who related rain in North-east Brazil to temperature gradient in the North Atlantic. Another more general relationship follows briefly.

The temperature gradient determines the degree of baroclinic eddy activity which in turn controls the flux of angular momentum polewards. As the latter increases the Hadley cell circulation must also increase in order to provide a momentum balance in the upper troposphere at low latitudes. A strong polewards flow there, which is acted on by the Coriolis torque to produce an acceleration towards the east and thereby a balanced situation, is best achieved with the rising motion to the south of the equator as in the present January case. The suggestion here is that this situation prevailed at 20,000 BP.

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Measurements on a Negative-Thixotropic Fluid

I HAVE carried out some measurements on an alkaline perbutan latex dispersion which shows distinctive negative-thixotropic properties. The latex is normally a milky fluid but, when vigorously shaken, rapidly turns into a gelatinous mass. On resting it reverts to fluid in 15 to 30 min depending on the concentration.

There have already been some descriptions of negative-thixotropic behaviour¹⁻¹¹, but few authors have demonstrated the recovery of the fluids involved at rest.

I used a Weissenberg rheogoniometer with a 75 mm 2° cone-and-plate arrangement. It was sheared at a series of increasing shear rates D at 25° C. Each D was held for about 10 s until the torque reading seemed to be constant. At low D the shear stress, F , results showed no untoward behaviour. The flow curve closely obeyed the power law equation with an index of 0.9 over about three decades of shear rate from 0.1 to 100 s⁻¹. But at high D , typically about 200 s⁻¹, and after a time at an apparently constant value, F began to rise, and in about 1 min went off scale. The latex in the cone-and-plate gap formed into little nodules and was expelled.

I examined this shear thickening behaviour by plotting the shear stress/time (F, t) relationship at constant D . There was much variation in the time of shearing required at any particular D before a sample would show shear thickening. For each (F, t) curve a time, t_c , was chosen in a subjective manner as the point at which the shear thickening begins. The dependence of t_c on D is shown in Fig. 1B. Using this time as zero, the (F, t) curves for each D were aligned so that the dependence of the shape of the curves on D was brought out (Fig. 1A). It can be seen that in spite of the large variation in t_c , the aligned curves show close agreement. For low D the rise in F with t was gradual but at high D the increase in F can be described as catastrophic once t_c was exceeded. This behaviour is similar to that described by Pavan *et al.*¹⁰ and Savins¹¹ but I was unable to obtain the higher steady F values because the sample was expelled.

I tried to map the constant-structure (λ) curves of Cheng and Evans^{12,13} using the experimental technique of step change in shear rate. In spite of the variability in the latex samples, even in those taken from the same 50 ml batch, and other difficulties, for example, solvent evaporation if the sample was used for too long and loss of

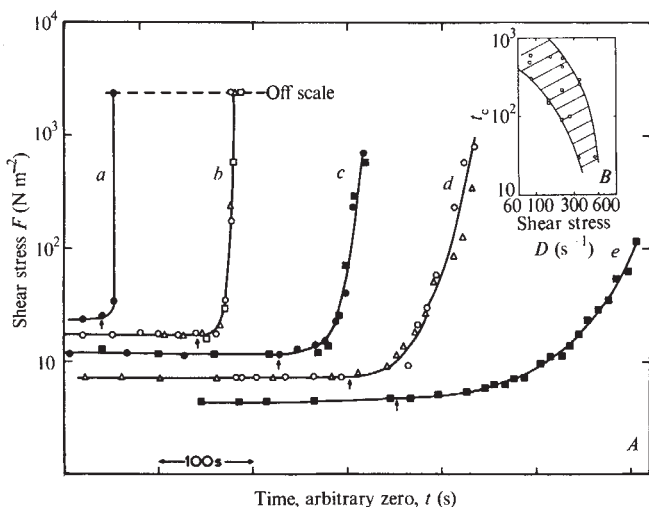


Fig. 1 A, Shear stress/time curves at various shear rates aligned with t_c as zero. $\uparrow$, Time at which shear stress starts to increase. a, 534 s⁻¹; b, 337 s⁻¹; c, 212 s⁻¹; d, 134 s⁻¹; e, 84.5 s⁻¹. B, Shear rate dependence of t_c .

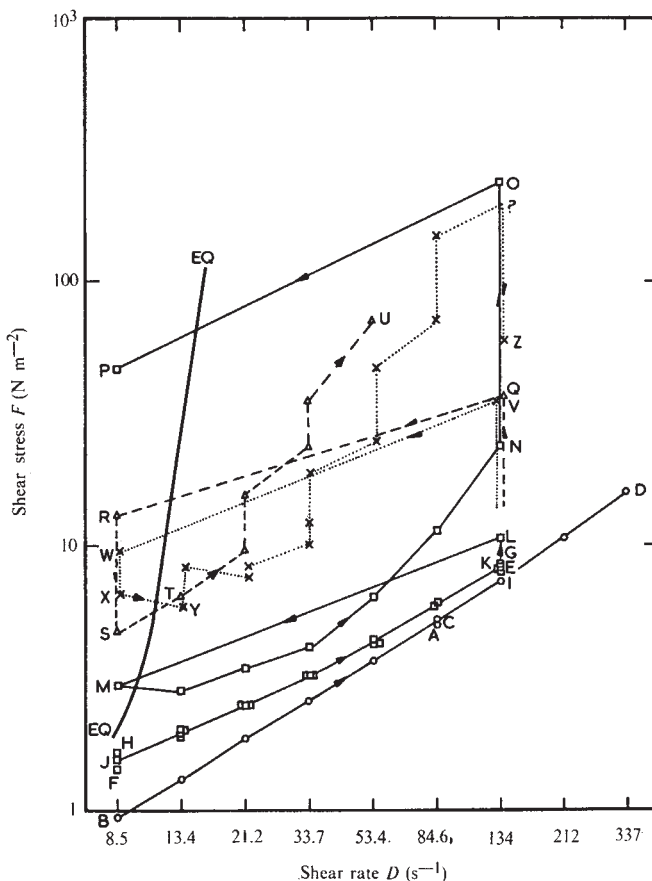


Fig. 2 Results of experiments to map the constant- λ structure curves (see text for explanation). Samples tested: $\circ$, first; $\square$, second; $\triangle$, third; $\times$, fourth.

sample by expulsion, a clear picture emerged (Fig. 2). One latex sample was sheared at 85 s⁻¹ for 720 s without F increasing appreciably (point (A) in the figure). The value of D was suddenly decreased to 8.4 s⁻¹ (B), and then increased by steps back to (C) and beyond to 337 s⁻¹ (D). The F value on reshearing at C was virtually the same as that at the start but at 534 s⁻¹ the sample was expelled immediately.

A second sample was sheared at 134 s⁻¹ for a time (E) and then repeatedly sheared over a range of values of D (F to G, H to I, J to K) for a total of 1,020 s without significant increase in F . In the next 57 s at 134 s⁻¹ F did, however, rise significantly (L) and a different set of results was obtained when the cycle was repeated (M to N). The value of F increased further when D was held at 134 s⁻¹ (O) and on changing down to 8.5 s⁻¹ a large F was obtained (P).

The behaviour of the sequence (LMN) was examined in more detail with a third sample. This was sheared at 134 s⁻¹ and reached Q. On changing to 8.5 s⁻¹, F decreased with time (R to S). Nothing special was noted at T, but at the two higher values of D , F was observed to increase with time when D was held steady for a short time. On reaching U the sample was rapidly expelled. The same experiment was carried out on a fourth sample with the result also shown in Fig. 2 (VWXY to Z): it was not expelled until 134 s⁻¹ was reached.

The results of Fig. 2 show the trend of the family of constant- λ curves in the curves (BCD); (GF, HI and JK); (LM, OP, QR and VW). Judging by the shape of the curves (GF), (HI) and (JK), it can be conjectured that the constant- λ curves show yield stresses which increase as the level of structure increases. The position of the equilibrium curve (EQ) is approximately as shown. It

The constant- λ curves of Fig. 2 and the (F,t) curves of Fig. 1 are used to determine the two negative-thixotropic functions $\alpha(F,D)$ and $\beta(F,D)$ as defined by Cheng^{14,15}.

$$\alpha(F, D) = (\partial F / \partial D)_\lambda; \quad \beta(F, D) = (\partial F / \partial t)_D$$

From this line of reasoning it might be conjectured that the temperature dependence of negative thixotropy is opposite to that of thixotropy. We therefore tested the

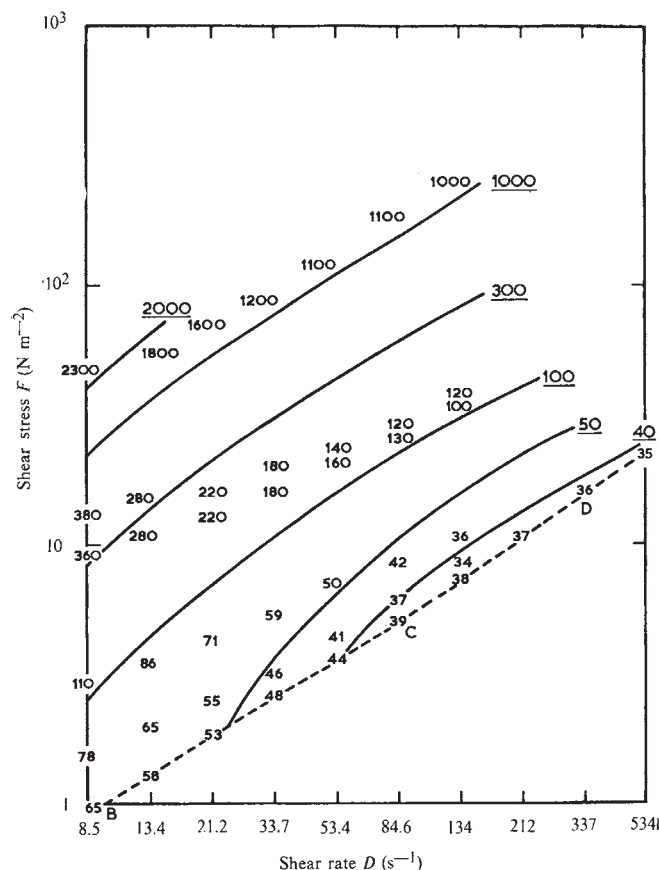


Fig. 3 Map of constant- α curves. α is given in $10^{-3} \text{ N s m}^{-2}$.

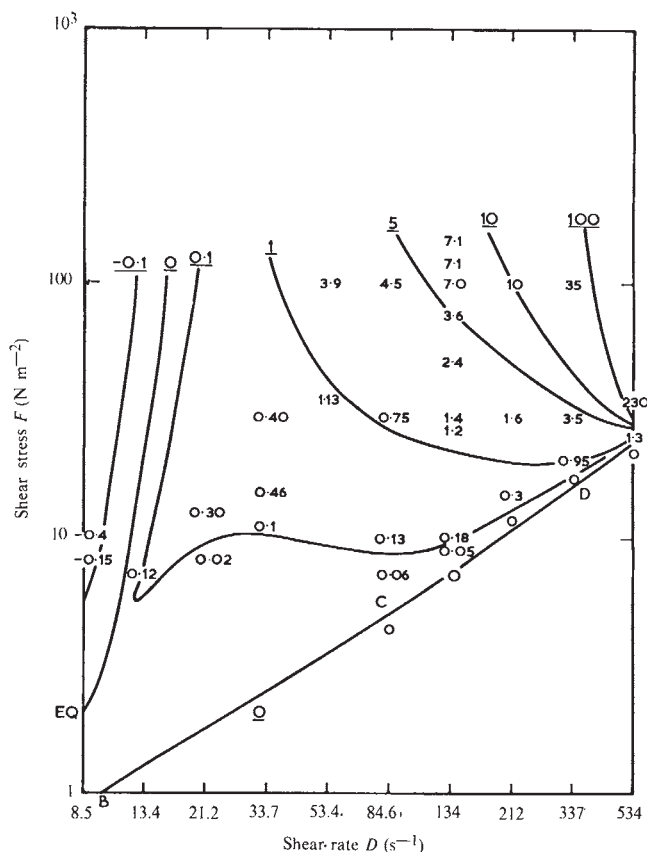


Fig. 4 Map of constant- β curves. β is given in $\text{N m}^{-2} \text{s}^{-1}$.

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Can Ball Lightning Exist in a Vacuum?

BLAIR¹ has suggested that ball lightning is associated with a strong magnetic field which extends far beyond the confines of the ball.

I have been within 50 cm of ball lightning in its smooth and unerring passage through an aircraft^{2,3}. I carried a penknife in my trouser pocket, a steel tobacco tin in my left jacket pocket and a steel screwdriver in my right jacket pocket. No motion of these objects was detected although they were known to be satisfactory detectors of magnetization and would have been greatly moved by a field of 150 gauss whether centred on the ball or otherwise directed through the aircraft. Noting also the ethereal quality of ball lightning, it is surprising that, if it is strongly coupled to a magnetic field as Blair suggests, the balls did not dance to the bells¹.

In recent years I have received several first hand reports on ball lightning. These include an event where the ball appeared some seconds before a nearby building was struck with lightning. The ball had the classical diameter of ~20 cm and maintained a flight path about 50 cm above the local surface (a staircase and subsequently the flex of a vacuum cleaner held in the mouth by the transfixed observer). A further important observation was of a 20 cm ball which appeared at a height of about 50 cm over the trailing edge of the mainplane of an aircraft in flight. It moved parallel to the line of the mainplane at a speed of about 1 m s⁻¹ before being cast off the end and was not blown off in spite of the considerable air speed. There are other reports where the velocity of a ball external to an aircraft is quoted as comparable to that of the aircraft and not that of the air through which it is moving.

As I pointed out in my review of Singer's book⁴, if one rejects sightings which are contradictory or highly questionable as scientific observations, the same salient features of ball lightning recur in all reliable reports. In particular, the diameter of the ball, the velocity relative to the local surface, the distance from the surface and the lifetime of the ball are remarkably consistent. On the whole the reports of benign ball lightning tend to be more reliable than those of the explosive variety which may be confused with meteorites and other energetic phenomena.

I suggest that ball lightning is dependent not on the vaporization of a surface but on the formation of a phase-locked loop of electromagnetic radiation in the intense field associated with lightning activity. I further suggest that there is, in these circumstances, a particular wavelength of electromagnetic radiation which can form a stable standing wave which externally exhibits a spherical configuration and which excites the ambient gas to produce the glow by which it is seen. As the energy is dissipated in this manner the lifetime of the ball is limited but the locking of the wavelength maintains its configuration and its dimensions. It follows that the typical clearance of the ball from conducting surfaces may be associated with the maintenance of equilibrium between the ball and its image in the conductor.

Although the scale and degree of quantization of the phenomena are quite different, the occurrence of electro-

magnetic radiation in phase-locked loops at a precise frequency also occurs in the process of pair production.

There are at present a few reliable reports, but it will be very interesting to accumulate further reliable data with which to show that the size of a ball is, to a first order, independent of the pressure of the air. In particular, it may be possible for ball lightning to exist in regions of very low pressure where it may not be recognized by the luminosity of excited gas.

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BIOLOGICAL SCIENCES

Ribosomal DNA Connectives between Human Acrocentric Chromosomes

ASSOCIATION of satellite regions of the human acrocentric chromosomes 13, 14, 15, 21 and 22 has received much attention because of its possible relation to nondisjunction, translocation and lesser structural variations, to which these chromosomes seem unusually prone. (A list of references relevant to this subject is available from the authors.) The overall frequency of associations in metaphase varies with techniques of cell culture and preparation as well as with the individual¹⁻⁴. The participation of different acrocentric chromosomes is random in some people, but nonrandom in others³⁻¹³. As individual variation may account, in part, for contradictory reports concerning correlation of association characteristics with age^{14,15}, sex^{4,14,17,18} and chromosomal abnormalities^{10-14,18-22} it is an important feature to explain.

Threads connecting satellites are occasionally visible; for example, Zang and Back⁴ noted that about 10% of their associations were fixed in this manner. By electron microscopy, Lampert *et al.*²³ showed that intersatellite fibres—in common with other connectives—consist of type B nucleoprotein, the usual structural component of condensed chromosomes. A large bundle of such fibres would be required to produce a visible thread; from this it can be surmised that connectives are more often present than seen. In the course of experiments on hybridization of tritium-labelled rRNA (³H-rRNA) to human metaphase chromosomes²⁴ we found grains arranged between separate satellites, indicating the presence of subvisible labelled strands. Thus intersatellite connectives are indeed more frequent than they seem to be, and their nucleic acid is identified as DNA complementary to rRNA (rDNA). This identification suggests a hypothesis to explain individual variation in human satellite associations.

We used a modification of the *in situ* hybridization technique of Gall and Pardue²⁵. Human ³H-rRNA of specific activity 4 × 10⁶ d.p.m. μg⁻¹, at a concentration of 2 μg ml⁻¹ in 4 × SSC, 50% formamide, was applied to slides on which the DNA of human lymphocyte chromosomes had been denatured in 95% formamide. The slides were held for 18 h at 38° C, washed, treated with RNase, dried, coated with Kodak NTB 2 emulsion and exposed for 1 month. The ³H-rRNA was accompanied by excess unlabelled bacterial RNA to compete for nonspecific binding. After development, the slides were stained with Giemsa. Details of

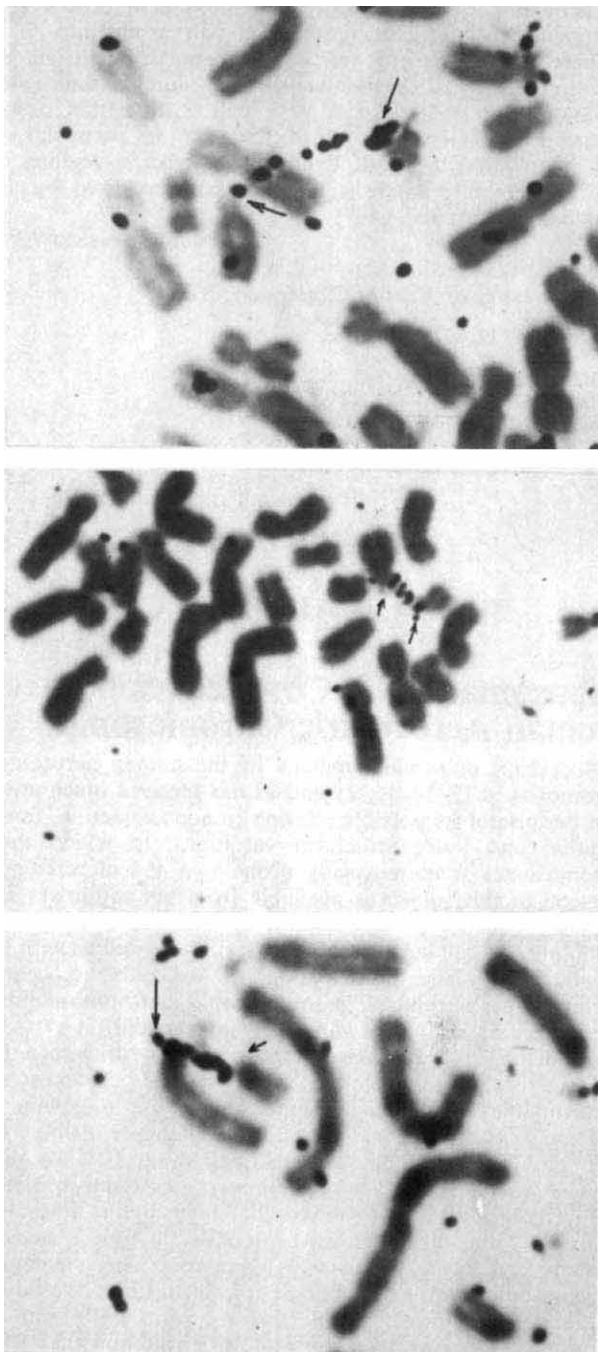


Fig. 1 Portions of metaphase figures showing autoradiographic evidence of connectives following *in situ* hybridization with ^3H -rRNA. Arrows indicate satellite regions of the acrocentric chromosomes involved.

^3H -rRNA preparation and hybridization on slides are given elsewhere²⁴.

Examination of 105 metaphases revealed eighteen cases in which lines or arcs of grains connected the satellite regions of different acrocentric chromosomes, although no visible connectives were present. In a larger number of cases subvisible strands were suspected; but we were not convinced of their reality, because the grain density tended to decrease with increasing distance between acrocentrics. Figure 1 shows examples in which connectives may be inferred with varying degrees of confidence. Unequivocal connectives were present where the chromosomes would not have been considered associated in the absence of grains. The number of grains per connective was within the range observed over satellite associations. In no case did any array of grains

with obvious serial correlation terminate on any chromosome other than those of the D and G groups.

It is clear from cytological evidence²⁶, and from the presence of rDNA²⁴, that each of the acrocentrics—and no other chromosome—possesses a nucleolar organizer. Association of satellites in metaphase is therefore generally regarded as a holdover from their proximity to a nucleolus. The question remains, however, of why such proximities persist when the chromosomes are spread on slides. When chromosomes condense and nucleoli disappear, the rDNA previously dispersed in nucleoli is seen to be concentrated in satellite regions²⁴. As the amount of rDNA in the human genome²⁷ is such that its uncondensed length would average more than 200 μm in each of the acrocentric chromosomes, the rDNA evidently must condense at some time during chromosome condensation. Strand proximity within a nucleolus affords an opportunity for entanglement, or shared nucleoprotein complexing, or rDNA from different nucleolar chromosomes. We surmise that such co-condensation gives rise to connectives among the satellites. In consequence, residual proximities would be rendered more or less stable, depending on the ductility and elasticity of connectives, and the forces displacing chromosomes during the preparation of slides. This interpretation is consistent with the presence of both visible and subvisible connectives stretched to various degrees, and with partial dependence of the frequency of associations on the method of preparation. The hypothesis to be advanced is based on the inference that those associations that persist into metaphase are, in most cases, maintained by nucleoprotein connectives containing rDNA.

To explain individual variation, we propose that the frequency with which connectives involve the rDNA of a given nucleolar organizer is a function of its rDNA content. The overall association frequency is thus determined, in part, by the total amount and distribution of rDNA, while the individual specific pattern is determined by the distribution alone. Accordingly, in a person with random association of different acrocentrics, each nucleolar organizer would have approximately the same amount of rDNA; whereas in persons showing nonrandom association, some of the nucleolar organizers would contain unequal amounts of rDNA. Because the association frequency is sensitive to culture conditions^{1,2}, it may be difficult to correlate with total rDNA content. According to our hypothesis, however, individual specific patterns should be practically free from technical variation. Detection of major inequalities in rDNA content among different nucleolar organizers is feasible by means of grain counts after *in situ* hybridization with ^3H -rRNA.

The hypothesis implies that the iteration number of the rDNA is polymorphic, and is a heritable attribute of a given nucleolar organizer, as already demonstrated in *Xenopus*²⁸ and *Drosophila*²⁹. It predicts that satellite association patterns are heritable in a complex way. As the normal complement of acrocentrics is any of 1,024 combinations of the parental chromosomes, this prediction cannot be tested in unselected pedigrees. With probands selected for extremely nonrandom association, it should be possible to trace the inheritance of chromosomes that contribute largely to non-randomness. Concordance of association characteristics in monozygotic twins is expected, but only insofar as the amount and distribution of rDNA are stable in somatic cells.

Observations that parallel these predictions have been reported with respect to morphological features of satellite regions; that is, they show individual variation³⁰⁻³⁶, concordance in monozygotic twins³⁷, and marker chromosome transmission. (A list of references relevant to marker chromosome transmission can be obtained from the authors.) It is uncertain, however, whether rDNA content, or tendency to associate, can be regularly correlated with satellite morphology.

It is hard to avoid the question of what happens to the connectives at division. We surmise that they can unravel; but their breakage is a possible source of variation in rDNA content and distribution, and—according to our hypothesis—in the association characteristics. The existence of individual specific patterns suggests that such variations do not originate often enough to cause significant heterogeneity among somatic cells. No definitive investigation of the long term stability of satellite association patterns has been reported.

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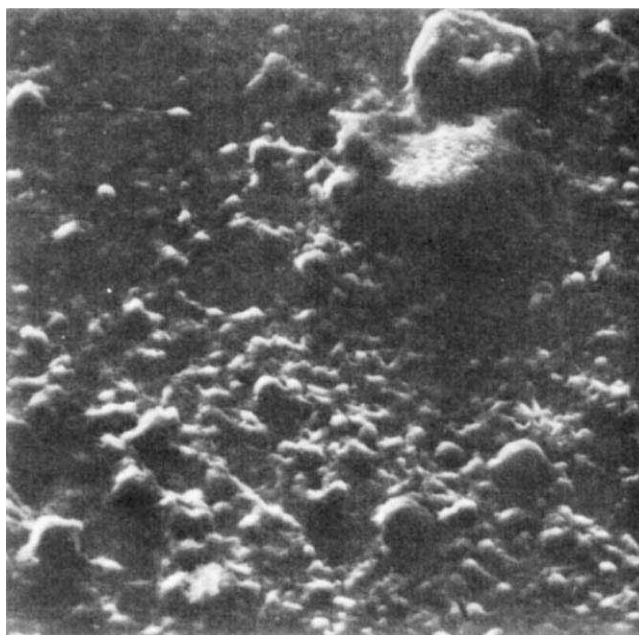


Fig. 1 Scanning electron micrograph of small T mycoplasma colonies originating from sperm cells. (Magnification $\times 1,380$.)

in abundance from the ejaculates and the cervical secretions of a selected group of patients with unexplained infertility³. It has been suggested that the T mycoplasmas might play an important part in reproductive failure, as pregnancies were achieved in about 30% of the couples after eradication of the T mycoplasmas⁴. The possible underlying mechanism remained obscure although some data indicated that the T mycoplasmas were attached to sperm cells³. The work reported here was done to establish whether T mycoplasmas could be found attached to sperm cells of men with reproductive failure.

Sperm samples were obtained from infertile men with T mycoplasmas and from fertile men without T mycoplasmas in their ejaculates. One portion of the sperm specimen was inoculated into Shepard's U9 broth, transported to the laboratory, reinoculated and incubated⁵. One portion of the remaining specimen was washed four times in phosphate-buffered saline (PBS). The washed spermatozoa and the supernatants were inoculated onto Shepard's A3 agar and incubated³. The plates were read in a phase contrast microscope at $\times 320$ and the percentage of colonies selected at random originating from the spermatozoa was estimated. Some of the plates were then fixed in 2.5% glutaraldehyde–5% sucrose solution and then dehydrated in increasing concentrations of alcohol as described by Greenwood and O'Grady⁵. They were then gold shadowed and examined in a 'JEOL' JSM-3 scanning electron microscope at magnification up to $\times 5,000$.

The remainder of some specimens was diluted in PBS and then fixed in 2.5% glutaraldehyde. The specimens were then dehydrated in increasing concentrations of acetone and prepared for scanning electron microscopy. Single spermatozoa were examined in the 'JEOL' JSM-3 scanning electron microscope. Seminal cultures from seven men with a known T mycoplasma infection exhibited growth in six of the cases. Five controls showed no growth. Phase contrast microscopic determinations of the percentage of T mycoplasma colonies originating from the spermatozoa of five of the six positive cases are summarized in Table 1. Scanning electron microscopic examination revealed that the T mycoplasma colonies seemed to originate from the anterior or middle piece of the spermatozoa (Figs 1 and 2). Scanning electron microscopy of single, washed spermatozoa from infertile

T Mycoplasmas on Spermatozoa and Infertility

T MYCOPLASMAS have been associated with spontaneous abortions and stillbirths¹. In at least one case T mycoplasmas were the aetiological agents of amnionitis and spontaneous abortion². Recently we isolated T mycoplasmas

patients with growth of T mycoplasmas showed that some of the spermatozoa had rounded, bud-like outgrowths on the posterior part of the sperm head or on the middle pieces (Fig. 3). These bud-like outgrowths were not found in control specimens.

Table 1 Microscopic Determination of the Origin of Randomly Selected T Mycoplasma Colonies Isolated from the Seminal Fluid of Five Infertile Men

Patient code	No. of T mycoplasma colonies		Total number
	Origin from spermatozoa	Origin elsewhere	
PB	288 (93)	22	310
SN	280 (92)	25	305
JZ	232 (97)	8	240
FH	170 (85)	30	200
AP	200 (95)	10	210

Figures within parentheses denote percentages.

The results of this investigation suggest that T mycoplasmas are attached to sperm cells, in agreement with our earlier suggestions³. Similar findings have also been obtained with bull ejaculates by Taylor-Robinson and Manchee⁶. Whether the T mycoplasma cells adhere to the sperm cells during the passage of the ejaculate through the urethra, or earlier, was not possible to determine.

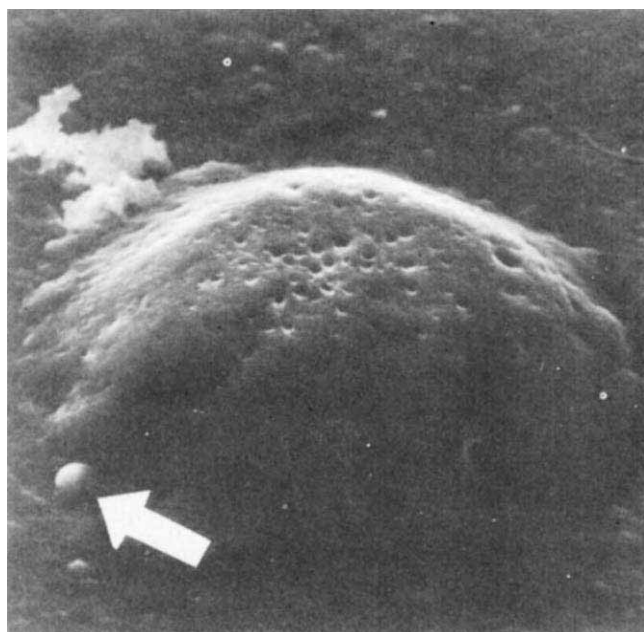


Fig. 2 Scanning electron micrograph of a T mycoplasma colony growing from the midpiece region of a sperm cell. Arrow, sperm head. (Magnification $\times 1,860$.)

Earlier reports^{6,7} showed that although T mycoplasmas were uniformly sensitive to doxycycline, the same T mycoplasma strain was easier to eradicate in the male than in his female partner. This is in accordance with the above findings as tetracyclines are bound to sperm cells and in particular to their midpiece regions⁸.

Some T mycoplasma strains produce substances which react with neuraminidase antibodies (H. G., unpublished). Pregnancy can be inhibited in mice after neuraminidase treatment⁹ and it is therefore possible that T mycoplasmas which produce neuraminidase-like substances may interfere with fertilization or development of the fertilized egg. This

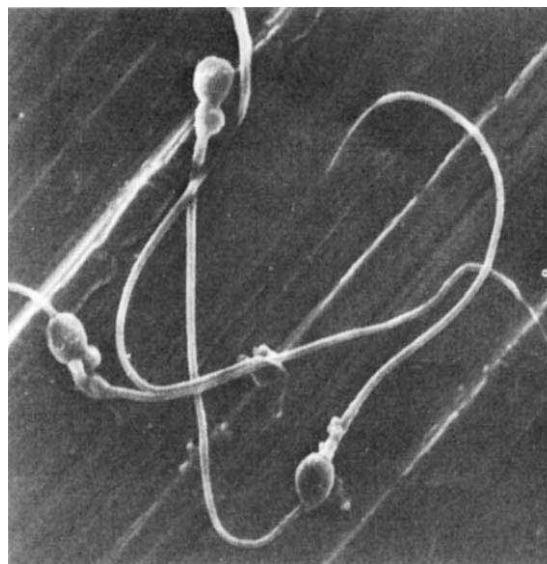


Fig. 3 Scanning electron micrograph of isolated spermatozoa from infertile patients with growth of T mycoplasmas. The bud-like outgrowths in the neck region were not seen in control preparations. (Magnification $\times 1,860$.)

may be the underlying cause for reproductive failure in some cases. Further investigations are now in progress.

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Histones and Cancer Test

IN 1967, Tomasi and Kornguth¹ described the purification and partial characterization of a basic protein from pig brain which they later² suggested was a new tissue specific histone. This was a reasonable assumption considering the general properties of the molecule but it would now seem likely that this protein is in fact one of the basic proteins of myelin. It is now reasonably well established that it is the basic proteins extracted from myelin which are responsible for the experimentally induced allergic encephalomyelitis in animals³, and Bauer⁴ has recently suggested that there is statistical evidence for the homology of the main determinant of the human encephalitogenic protein (residues 112-122)⁵ and a part of the amino acid sequence of the histone fraction F2A1. The similarity between the amino acid composition of the myelin basic protein and histones has been noted² and the differences stressed⁵, but

there can be no doubt that they are quite different proteins. Careful examination of the analysis given by Caspary and Field⁶ of their encephalitogenic protein of human origin and the purified histone fraction F2A1⁷, however, reveals a remarkable similarity. This being so, and because of the importance of the macrophage electrophoretic mobility (MEM)⁸ test, which may indicate the existence of malignant neoplasia particularly at an early stage of development, and because of the interest in the isolation of the tumour specific basic protein⁹, we thought it advisable to test the various histone fractions for their effect in this system. The five histones used were highly purified fractions prepared and characterized by methods which have all been described previously¹⁰. They were tested as described by Pritchard *et al.*¹¹ and the results are given in Table 1.

Table 1 Effect of Various Histone Fractions on Macrophage Electrophoretic Migration

"Antigen"	Slowing of macrophages (%)
Encephalitogenic protein	14.0
Histone F2A1	23.6
Histone F2A2	21.3
Histone F1	18.9
Histone F3	12.5
Histone F2B	6.1

The macrophage electrophoretic mobility (MEM) test was carried out according to the method of Pritchard *et al.*¹¹.

The various histones have been compared with the encephalitogenic protein prepared according to the method of Caspary and Field⁶ and it can be seen that the lymphocytes, which were from a patient with a squamous carcinoma of the cervix uteri, respond to histones F2A1 and F2A2 to a greater extent in these conditions. There are striking sequence similarities between these two histones¹². Histone F1 is about as effective as the encephalitogenic protein but histone F2B is relatively inactive. These results prompt many important questions. Does the fact that F2A1 gives better results than the encephalitogenic protein mean that the lymphocytes are "sensitized" to histones, and if so, why are the lymphocytes of cancer patients so "sensitized"? Are histones, or more specifically, histones F2A1 and F2A2, being released from tumours but not from normal cells and in this way inducing an autoimmune reaction? Is the sequence homology of histone F2A1 with the tumour antigen simply closer than with the encephalitogenic factor?

Further experiments are being carried out using protamine, polylysine, polyarginine and fragments of histone F2A1 but these initial results are given because of their apparent relevance to the MEM cancer test.

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Accelerated Substrate Cycling of Fructose-6-phosphate in the Muscle of Malignant Hyperthermic Pigs

THE syndrome of malignant hyperthermia can be induced in susceptible humans¹ and pigs by a variety of agents, such as halothane² and succinyl choline³. In swine, the syndrome is well documented⁴⁻⁶ and its onset is characterized by a sharp rise in body temperature which is often associated with muscle rigor. One of the most interesting biochemical responses in hyperthermia is the progressive loss of muscle ATP⁷ and/or creatine phosphate⁸ and the concomitant accumulation of P_i in the blood⁵.

Recent studies⁹ show that in bumble-bee flight muscle, the cycling of fructose-6-phosphate through reactions catalysed by phosphofructokinase and fructose diphosphatase (Fig. 1) is a possible means by which the insect generates heat to maintain thoracic muscle temperature at that required for flight. Uncontrolled cycling of fructose-6-phosphate could possibly give rise to the observed heat production and changes in ATP and P_i during hyperthermia. On this basis, we have investigated the rates of substrate cycling in halothane sensitive and non-sensitive pigs. A relationship is demonstrated between heat production induced by halothane and an accelerated rate of substrate cycling of fructose-6-phosphate in hind limb muscle of malignant hyperthermic pigs. Analysis of fresh muscle tissue indicates a seven-fold excess of fructose diphosphatase by comparison with the estimated rate of substrate cycling.

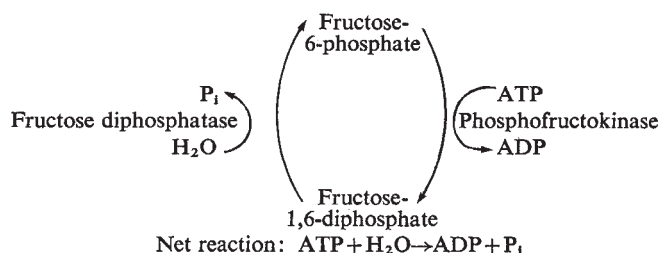


Fig. 1 Substrate cycling of fructose-6-phosphate with hydrolysis of ATP.

Pigs of either Hampshire (H), Poland China (P) or Poland China-Hampshire (HX) cross-strain were initially identified as hyperthermic or nonhyperthermic by their response to a short challenge with 3% to 4% halothane⁶. Animals were fasted for 16 h before surgery. Anaesthesia was induced with intraperitoneal thiamylal sodium, and the trachea was intubated using a Davol clear plastic tube that was attached to a Foregger anaesthetic machine. Anaesthesia was maintained using a mixture of N₂O, 4 l min⁻¹, and O₂, 2 l min⁻¹. Respiratory

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CO₂ was trapped in a CO₂ absorber. When required, N₂O was withdrawn and replaced by halothane (2%, v/v) in oxygen. Hind limb muscle, rectum, external iliac vein blood and aortic blood (at the level of the renal artery) temperatures were monitored by indwelling thermocouples (accuracy $\pm 0.05^\circ\text{C}$).

Figure 2a shows a typical temperature profile of control and hyperthermic pigs before and during halothane anaesthesia. The halothane-sensitive pigs had a distinctly higher body temperature before halothane administration. This may reflect their greater susceptibility to the stress of manipulation and premedication. The hyperthermic pigs responded with an increase in venous blood temperature flowing from the hind limb and clearly demonstrates that the muscle is a source of heat production. The difference between halothane sensitive and non-sensitive animals is most evident from plots of the V-A temperature difference (Fig. 2b) which is positive for the hyperthermic pigs and negative for the control pigs.

In the hyperthermic pigs, halothane caused a slight transient increase in ATP concentration which was followed by a marked decrease (Fig. 2c). The average rate of decrease in ATP concentration was approximately 0.1 μmol per g fresh weight per min. A compensatory increase in the concentrations of ADP or AMP did not occur, showing that there was a decrease in total adenine nucleotide concentrations. In agreement with previous observations the loss of ATP coincided with increased blood levels of P_i (ref. 5) and muscle levels of total inosine⁸. In the control pigs, halothane produced only marginal changes in nucleotide concentrations.

The results of Table 1 show that a relationship exists between the hyperthermic response and the rate of substrate cycling of fructose-6-phosphate. The method for determining the rate of substrate cycling of fructose-6-phosphate^{10,11} involves measuring the decrease in the ³H/¹⁴C ratio of cellular 5-³H,U-¹⁴C-hexose-6-phosphate. The excess of aldolase and triose phosphate isomerase in muscle will result in a rapid loss of tritium from 5-³H,U-¹⁴C-fructose-1,6-diphosphate by equilibration through glyceraldehyde-3-phosphate and dihydroxyacetone phosphate; therefore, operation of the cycle shown in Fig. 1 gives rise to an observed decrease in ³H/¹⁴C ratio of hexose-6-phosphate. There was a six to eight-fold increase in the rate of substrate cycling in sensitive animals following exposure to halothane and this increase was approximately proportional to the final rectal temperature (Table 1). In contrast, when non-sensitive animals were exposed to halothane, the rate of substrate cycling was minimal and unchanged. Thus, thirty to eighty-fold differences in the rates of substrate cycling were evident between sensitive and non-sensitive animals exposed to halothane.

In the susceptible pigs halothane increased the rate of muscle glycolysis 1.2 to two-fold. Following halothane, the glycolytic rate of the sensitive pigs' muscle was two to ten-fold greater than that of the non-susceptible animals in agreement with a halothane induced stimulation of glycolysis¹² in the muscle tissue of sensitive animals⁵.

Whereas there are marked differences in the calculated rates of substrate cycling in muscles of sensitive and non-sensitive animals that have been exposed to halothane (Table 1), inherent assumptions in the method used for the estimation of both glycolysis and substrate cycling^{10,11} have necessitated application of the isotope at a time corresponding to a new metabolic steady-state. As shown in Fig. 2a and b, isotope infusion was begun when V-A temperature differences were maximal and constant. It is therefore likely that metabolic events that result in the accumulation of lactate and that are detectable very early after exposure to halothane¹³ have already occurred before the measurements of cycling and glycolysis have been made. Thus, the results of Table 1 for the hyperthermic pig may be underestimates of the actual rates of carbon flux.

For substrate cycling to occur, it is essential that excess catalytic activities of phosphofructokinase and fructose diphosphatase are present. Muscle is a rich source of phosphofructokinase; however, early measurements of fructose diphosphatase

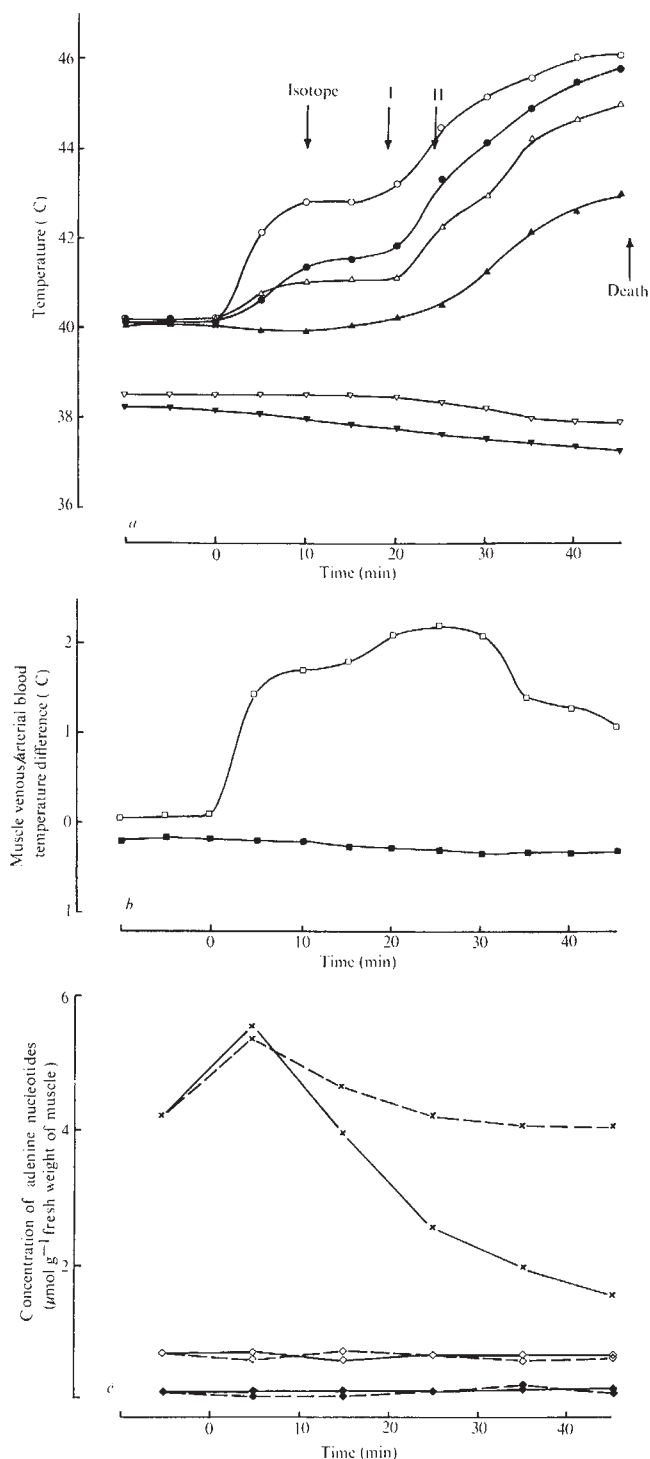


Fig. 2 Effect of halothane (2%) anaesthesia on blood and organ temperature, heat production by muscle and the muscle concentration of adenine nucleotides. *a*, Temperatures of halothane-sensitive pig HX-86-1: ●, muscle (gracilis and adductor); ▲, rectum; ○, venous blood; △, arterial blood. Organ temperatures of halothane non-sensitive pig H-14-9: ▽, muscle; ▾, rectum. Onset of muscle rigor: I, hind limb; II, fore limb. *b*, Difference between venous and arterial blood temperatures of muscle from halothane-sensitive pig HX-86-1 (□), and halothane non-sensitive pig H-14-9 (■). *c*, Halothane-sensitive and halothane non-sensitive pigs are represented by solid and broken lines, respectively. ×, ATP; ◇, ADP; ◆, AMP. Concentrations were determined on perchlorate extracts from freeze-clamped samples and are expressed as means from three animals in each group.

in this tissue suggested that it was present in only trace amounts¹⁴. The demonstration of appreciable activity¹⁵ and the recent isolation of muscle fructose diphosphatase¹⁶ in a

homogeneous form shows that this conclusion was premature. Assays of enzyme activities at 37° C in homogenates of muscle from hyperthermic pigs show that phosphofructokinase was present at $30.3 \pm 12.2 \text{ U g}^{-1}$ fresh weight and fructose diphosphatase at $3.1 \pm 0.4 \text{ U g}^{-1}$ fresh weight. These activities are in excess of the observed rates of substrate cycling shown in Table 1. The catalytic activities of aldolase and triosephosphate isomerase were $42.4 \pm 13.2 \text{ U g}^{-1}$ and $780 \pm 210 \text{ U g}^{-1}$, respectively, which is considered sufficient to catalyse a rapid loss of ^3H from $5\text{-}^3\text{H}, \text{U-}^{14}\text{C}$ -fructose-1,6-diphosphate¹⁰. Further, analysis of the activities of muscle phosphofructokinase, fructose diphosphatase, aldolase and triosephosphate isomerase showed that there were no significant differences between animals sensitive and non-sensitive to halothane. No large differences in the kinetic properties of fructose diphosphatase from these two sources could be detected.

Table 1 Effect of Halothane Anaesthesia on the Rates of Glycolysis and Substrate Cycling of Fructose-6-phosphate in Pig Muscle *in vivo*

	Final rectal temperature (°C)	Metabolic rate (μmol/min/g fresh weight)	Cycling of fructose-6-phosphate†
Halothane sensitive:			
Pig No. P-85-3, before halothane	39.3	0.10	0.05
Pig No. HX-86-4, after halothane	45.5	0.12	0.4
Pig No. HX-86-5, after halothane†	41.8	0.20	0.3
Pig No. HX-86-1, after halothane†	43.5	0.20	0.4
Halothane non-sensitive:			
Pig No. H-14-9, after halothane	36.7	0.06	0.01
Pig No. H-14-1, after halothane	36.8	0.02	0.005

Estimations of the rate of substrate cycling and the rates of glycolysis were made from measurements of the equilibrium $^3\text{H}/^{14}\text{C}$ ratio in $5\text{-}^3\text{H}, \text{U-}^{14}\text{C}$ -hexose-6-phosphate (R^h) and the rate of phosphorylation of fructose-6-P (F). The rates of glycolysis (G) and substrate cycling (S) are calculated from the equations^{10,11}

$$S = F(1 - R^h/R^g) \\ G = F - S$$

where R^g is the $^3\text{H}/^{14}\text{C}$ ratio in $5\text{-}^3\text{H}, \text{U-}^{14}\text{C}$ -glucose as the applied labelled substrate. $5\text{-}^3\text{H}, \text{U-}^{14}\text{C}$ -Glucose (0.5 mCi $5\text{-}^3\text{H}$ -glucose and 5 μCi $\text{U-}^{14}\text{C}$ -glucose in 0.52 μmol) was infused into the femoral artery at $0.052 \text{ μmol min}^{-1}$ for 10 min from an indwelling catheter. For halothane-sensitive animals, the infusion of isotope was begun following the initial signs of muscle temperature increase (see Fig. 2a, for example). Muscle biopsies were removed at 3, 6, 9, 12 and 15 min and frozen in clamps that were precooled in liquid N_2 . Frozen muscle (10–15 g) was homogenized in 3 volumes of 6% (w/v) HClO_4 . The homogenate was centrifuged at $8,500g$ for 15 min and the supernatant fluid was adjusted to pH 6.5 with 20% (w/v) KOH. Following the removal of the KClO_4 precipitate, the solution was applied to a column (10 cm × 0.5 cm) of 'Dowex' AG 1X8 borate resin (200–400 mesh). The neutral eluate was counted to determine tritium release to cell water (T) from which F is calculated⁹

$$F = \frac{T}{^{14}\text{C-specific activity hexose-6-P} \times ^3\text{H}/^{14}\text{C ratio of hexose-6-P} \times \text{time}}$$

The column was then eluted with 0.2 M ammonium tetraborate (20 ml) followed by 0.35 M ammonium tetraborate (20 ml). The later fraction containing chiefly glucose-6-phosphate and fructose-6-phosphate was treated to remove ammonium tetraborate⁹. The hexose-6-phosphates were purified by enzymatic conversion to fructose-1,6-diphosphate or by oxidation to potassium-6-phosphogluconate with iodine¹⁷.

* Estimated error is $\pm 18\%$ of the value shown.

† Animals which developed muscle rigor.

It is proposed from the present data that substrate cycling is an aberrant reaction in muscle from hyperthermic pigs and that this could contribute to the observed depletion of ATP and heat production during the hyperthermic syndrome.

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Infection and Transformation of Bovine Lymphoid Cells *in vitro* by Infective Particles of *Theileria parva*

TECHNIQUES recently developed in this laboratory can be used to infect cattle reproducibly with East Coast fever with infective particles of *Theileria parva* collected from the tick vector, *Rhipicephalus appendiculatus*. Infective particles can be collected either as *in vitro* tick feed material by inducing pre-fed, infected ticks to salivate into capillary tubes containing foetal calf serum¹, or as ground tick supernatant obtained by grinding the ticks in Eagle's minimum essential medium with Earle's salts (MEM) supplemented with bovine plasma albumin

(Fraction V from bovine plasma) (BPA) and collecting the supernatant².

When such infective material is inoculated subcutaneously into cattle the parasites may be detected as early as the 5th day after inoculation, when theilerial macroschizonts parasitizing lymphoid cells can be seen in Giemsa-stained biopsy smears from the local drainage lymph node. Infected lymphoid cells can be isolated and grown *in vitro*³ but infection of normal bovine lymphoid cell cultures has not so far been reported. We describe successful infection of such cell cultures using both *in vitro* tick feed material and ground tick supernatant.

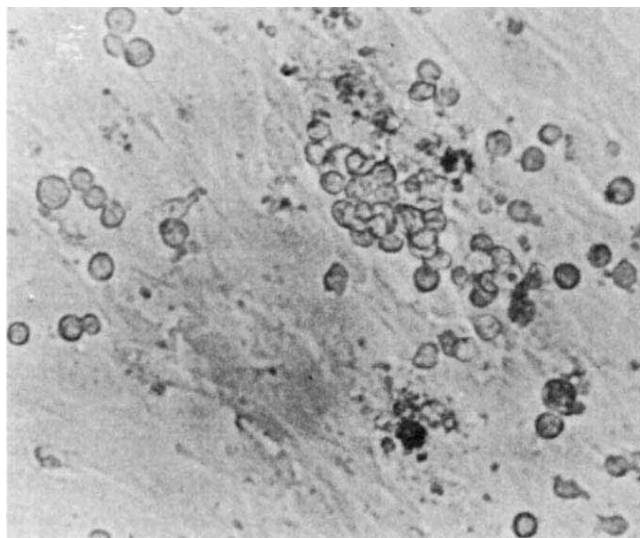


Fig. 1 Unstained mesenteric lymph node culture 26 d after inoculation with *T. parva* infective particles derived from *Rhipicephalus appendiculatus*. A small clump of refractile round cells associated with the fibroblastic monolayer is shown ($\times 300$).

Heparinized blood, spleens and mesenteric lymph nodes were obtained from three male calves less than 1 week old. Leukocytes were separated from peripheral blood as described by Aalund *et al.*⁴, and cells were teased from spleens and mesenteric lymph nodes. They were established as monolayers in small plastic "T" flasks using 6 ml MEM supplemented with 0.100 g l⁻¹ L- β -asparagine and 20% foetal calf serum. Penicillin 100 U ml⁻¹, streptomycin 100 μ g ml⁻¹ and kanamycin sulphate 100 μ g ml⁻¹ were added to the MEM which was further supplemented immediately before use with L-glutamine 0.29 g l⁻¹ (1 ml of a 200 mM stock solution per 100 ml of medium).

After maintenance for 2, 9 and 23 d, the supernatant was discarded and the cultures were inoculated with either *in vitro* tick feed or ground tick supernatant, each culture receiving material derived from the equivalent of fifteen ticks of the same infected batch. Control cultures received no inoculum. After inoculation all the cultures were overlaid with 6 ml of fresh growth medium containing nystatin 25 U ml⁻¹, and incubated at 37° C.

The medium in all cultures was changed once a week: the contents of each culture flask were placed in an individual centrifuge tube and the cells were sedimented by centrifugation at 180g for 5 min before being replaced in the culture flask with fresh medium. Once weekly, on a separate occasion, 2 ml (1/3 of the total volume of the medium) was removed from each flask and replaced by 2 ml of fresh growth medium. The sample taken was centrifuged at 180g for 5 min. Smears were made from the centrifuged cell pellet, stained with Giemsa and examined for macroschizont-infected lymphoid cells.

Infected lymphoid cells were observed 26 d after inoculation

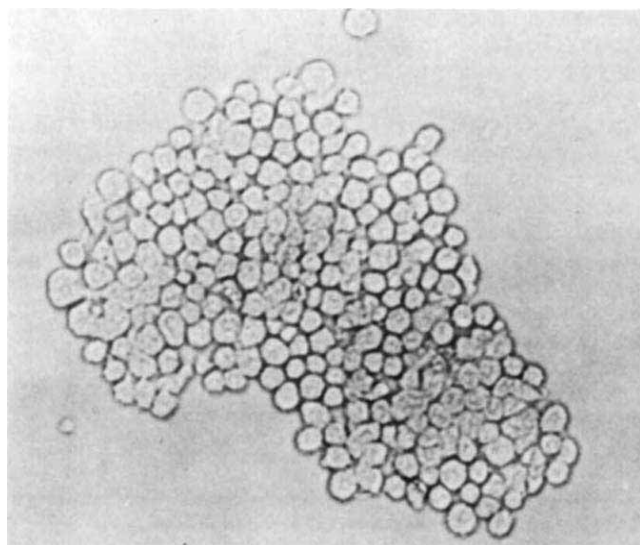


Fig. 2 A clump of transformed lymphoblastoid cells infected with *T. parva* macroschizonts, growing in suspension, originating from a mesenteric lymph node culture infected *in vitro* ($\times 300$).

in the 9 and 23-d mesenteric lymph node cultures receiving tick material. Cell lines have been established from these transformed cultures. No infection was detected in the 2-d mesenteric lymph node cultures nor in any of the other cultures. In the cultures in which infected lymphoid cells were detected, small clumps of refractile cells were seen in suspension or associated with the lymph node monolayer of the relevant culture. This phenomenon is typical of early transformation and has previously been described in transforming lymphoid cultures isolated from *T. parva*-infected steers^{3,5}.

The apparently non-infected cultures, together with the control cultures, were maintained for 12 weeks after inoculation. On d 48 post-inoculation schizonts were detected in one leukocyte culture from the 23-d culture series, but this transformation could not be maintained. All other cultures remained negative.

Our ability to study the bovine-dependent side of the life cycle of *T. parva*, *in vitro*, has thus been extended and experiments are continuing with mesenteric lymph node cultures to investigate the precise mode of infection. Furthermore, a potential method for the *in vitro* titration of infective material harvested from ticks is now available.

This work formed part of the Immunological Research on Tick-borne Cattle Diseases and Tick Control Project supported by the United Nations Development Programme, with the Food and Agriculture Organization as the Executing Agency, in cooperation with the East African Community. The project is also supported by the Overseas Development Administration of the United Kingdom, the United States Department of Agriculture, the International Atomic Energy Agency and the Pfizer Corporation.

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Effect of Blood Flow Velocity on Growth Rate of Platelet Thrombi

ACUTE thrombogenesis in a flowing bloodstream can occur on damaged tissues in the normal circulation, especially on exposure to collagen, and over surfaces of vascular prostheses and artificial internal organs¹⁻³. The thrombi are composed predominantly of platelets. Begent and Born⁴ have obtained quantitative data on growth rates of such thrombi produced *in vivo*.

Aggregation of platelets at a mural site involves biochemical and physical processes, and the growth rates are affected by the neighbouring blood flow field. Here I show that Begent and Born's results are consistent with a physical model of the aggregation process that incorporates salient features of platelet behaviour, and discuss some of the consequences.

Such thrombogenesis can be considered in two phases: an initial adhesion of platelets to a surface, and aggregation of platelets on other platelets. It is not yet clear how specific sites for adhesion arise on non-biological surfaces, but surface charge distribution and asperities seem significant; the adhesion may be initially independent of the surface⁵, following the adhesion of a protein layer. At a later stage it may be somewhat dependent on the material, but this would seem to affect the number of sites (per unit surface area) on which the thrombi of the type discussed here grow; there is no evidence available that it definitely affects the growth rates of such individual thrombi. Platelets that aggregate on other platelets release activating agents; the dominant component is probably ADP (ref. 6). The time-course of this release following aggregation is not known; however, it is known that release begins a few seconds after aggregation. The activating agents diffuse into the bloodstream from a mound of aggregated platelets; the Schmidt number for diffusion of ADP and similar molecules in blood is $\sim 10^4$, so even with small Reynolds number flows in arterioles and venules there will be a distinct concentration layer of activator surrounding the mound. The shape and size of this layer depend upon the velocity field^{7,8}. Bloodstream platelets follow paths which carry some of them into the activator concentration layer, which extends several microns into the flow. Stream platelets are activated rapidly by ADP and other activators⁹; the velocity of platelet response (the characteristic response time) is affected by temperature markedly and by ADP concentration, up to a certain concentration⁹. The initial activation by ADP is reversible, and reversal may also be quite fast. At least some of the activated platelets will be aggregated if they are close enough to the aggregate surface. This leads to fresh carpeting of the aggregate with platelets; a fresh layer may be completed in a few seconds. With further release of activating agents, an autocatalytic situation arises: the aggregation process has feedback.

In this sequence of events there are some features where quantitative information is not available, so that a precise theoretical prediction of thrombus growth is not yet possible. But it is possible to describe a simplified model that predicts observed behaviour.

Smoluchovski originated the theory of gradient coagulation, as described by Levich¹⁰. A comparison of the frequency of encounter by velocity gradient (taking values of the latter corresponding to Begent and Born's experiments) to that by Brownian motion gives a ratio of more than 10^3 , showing that a linear trajectory assumption is acceptable for the present problem. Possible scattering by erythrocytes is not likely to be significant over the short range of flow path for which the Smoluchovski theory is applied. I consider a platelet aggregate growing on a wall to have a semicircular cross-section normal to the wall, with maximum radius R_1 (at any instant in time) and y coordinate normal and x coordinate parallel to blood flow. The longitudinal section of the aggregate in the x direction is smooth and roughly semi-elliptic (the precise shape is not important). Stream-borne platelets approaching the activator concentration layer are assumed to have straight line trajectories parallel to x , and to be present in the stream with a uniform number density n_0 . The velocity v in the x direction varies linearly with y (i.e., $v = \Gamma y$), a good approximation near a wall under shear flow. All platelets (radius R_2) that have trajectories which pass into or graze the semicircle of radius R_1 are assumed to encounter the activator concentration layer and to become activated after a delay time t_A . Platelets then aggregate on the thrombus if they are still in its immediate vicinity; otherwise they escape. Platelets have transit times l/v , where l is a characteristic length of the aggregate in the x direction. This length depends on the shape of the aggregate, but if the shape remains steady in time with growth of the aggregate $l = \lambda(R_1 + R_2)$. Thus platelets will be aggregated if $\lambda(R_1 + R_2)/v > t_A$ but will escape if $\lambda(R_1 + R_2)/v < t_A$, with the latter effect appearing first, at a high shear rate, on the top of an aggregate where v is largest. The general expression for the aggregation frequency (number aggregated per second) is

$$N = 2\Gamma n_0 (R_1 + R_2) \cos\theta dy \\ = 2n_0 \Gamma (R_1 + R_2)^3 \int_{\theta_2}^{\theta_1} \cos^2\theta \sin\theta d\theta$$

where $y = (R_1 + R_2) \sin\theta$ and $v = \Gamma y$.

The upper limit $\theta_1 = \pi/2$ when $\lambda(R_1 + R_2)/v > t_A$, that is, when $\lambda/\Gamma t_A = 1/\Gamma\tau > 1$, but is $\sin^{-1}(\Gamma\tau)^{-1}$ when $1/\Gamma\tau < 1$. If $\theta_2 = 0$,

$$N = \frac{2}{3} n_0 \Gamma (R_1 + R_2)^3 F(\Gamma\tau)$$

$$F(\Gamma\tau) = 1 \text{ when } \Gamma\tau < 1 \\ = \{1 - [(1/\Gamma\tau)^2 - 1]^{3/2} / \Gamma\tau\} \text{ when } \Gamma\tau > 1$$

For a platelet aggregate growing with a steady shape the total number of platelets aggregated $\Sigma \approx \beta(R_1)^3$ and $d\Sigma/dt = N$; because N is proportional to $(R_1 + R_2)^3 \approx R_1^3$ (once thrombus growth is under way) the growth rate is exponential in time⁴, and the growth rate constant is $\frac{2n_0}{3\beta} \Gamma F(\Gamma\tau)$. Γ is proportional

to flow rate and a graph of $\Gamma\tau F(\Gamma\tau)$ against $\Gamma\tau$ demonstrates the effect of flow rate (Fig. 1). The similarity of this figure to Fig. 7 of Begent and Born⁴, giving the experimentally determined growth rate constants, suggests that the limitation in growth rate at higher velocities occurs through delay of platelet activation beyond the aggregate transit time rather than through shear stresses preventing adhesion. The down-sweeping part of the curve at larger $\Gamma\tau$ (Fig. 1) is changed if the thrombus cross-section is considered semi-elliptic with the major axis on the wall surface, instead of semicircular, but the effect is too small to be detectable with the present experimental data. The activation delay time seems to be in the range 0.1 to 0.2 s.

An additional comparison can be made for data where $\Gamma\tau < 1$, using the experimental value of n_0 , assessing Γ as $8\bar{v}/d$ (where $\bar{v}$ is the mean blood velocity and d is the venule diameter) and so on; although the shape factor β is not really

determined, and may vary somewhat with Γ , agreement with observation can be obtained using a plausible estimate.

To account for the lack of platelets with centres closer than R_2 to the wall $y=0$, the lower limit of integration should be changed to $\theta_2 = \sin^{-1}(\gamma + 1)^{-1}$, where $\gamma = R_1/R_2$. With large γ (large aggregates), θ_2 is close to zero. With small γ and large Γ , θ_2 may be larger than θ_1 , and no growth would be possible. A "skimming layer" essentially free of platelets may exist near the wall with large Γ , but a simple estimate for it as a function of Γ is not possible at present¹¹. Although the model described here does allow that the thrombus growth rate is zero at high enough Γ (ref. 4), it is not yet possible to prescribe the conditions where this occurs.

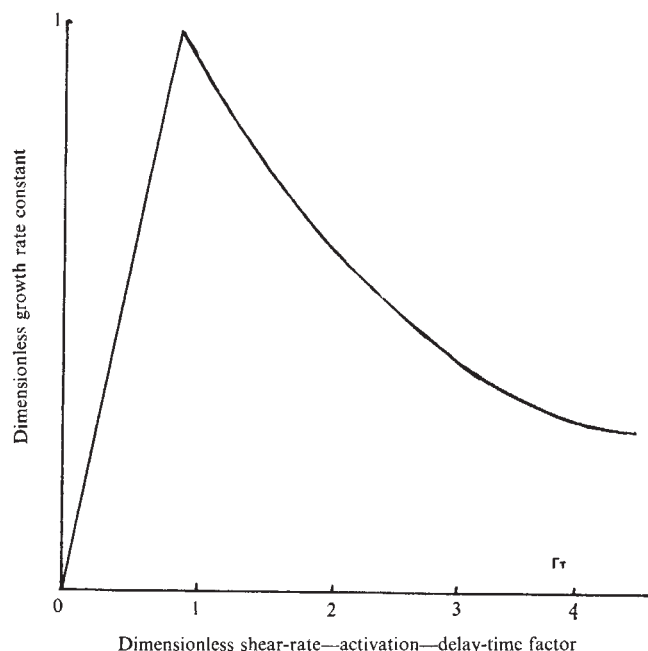


Fig. 1 Growth rate constant of platelet thrombi as a function of $\Gamma\tau$, where Γ is the velocity gradient of blood flow by a wall and τ is proportional to the activation delay time of unaggregated platelets.

My analysis gives an estimate of platelet thrombus growth rate based upon a hypothesis concerning the role of platelet activation delay time. It treats growth grossly and does not seek to predict the platelet aggregation pattern over the aggregate surface. The hypothesis can be tested by performing further experiments with iontophoresis of activators into venules with measured changes in temperature, or with a variety of species, coupled with separate determination of activation delay times, for example. The delay time t_A is probably distributed about its mean.

A growing thrombus is not the only possible source of activators. If blood undergoes suitable traumatic experiences, the erythrocytes can serve as sources of ADP even though damage may not be sufficiently severe to cause haemolysis. Activation of platelets from stream sources eliminates the wait for activation during transit of an aggregate and t_A has effectively become zero, at least until a reversal of activation occurs. Thrombus growth could be particularly vigorous. There is often acute (and ultimately occlusive) white thrombus growth in regions just downstream of manifolds or other places where the blood is fluid-dynamically agitated¹².

Monsler, Morton and Weiss¹³ have summarized work performed on thrombus formation at a stagnation region on non-biological surfaces. The physical extent of their thrombi is much greater (more than $10^3 \mu\text{m}$) than those analysed here, but their thrombi are speckled with clumps that may grow individually in a similar way.

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Formation of Nitrosamines in a Meat Curing Mixture

TRACE amounts of certain N-nitrosamines, well known carcinogens, in foods, especially nitrite-treated meat and fish products, have caused a great deal of concern¹⁻³. These compounds are usually formed from the interactions of nitrite and secondary or tertiary amines⁴⁻⁵. Recent studies, however, have shown that certain naturally occurring quaternary ammonium compounds can also react with nitrite to form nitrosamines⁶. Of the known nitrosamines dimethylnitrosamine (DMN) and nitrosopyrrolidine (NPY) are the two compounds which have been most frequently found to be present in cured meat products^{2,3,7,8}. NPY is formed during frying of bacon but its presence in other cured meat products has not been reported.

Table 1 NPY and NPi in Mettwurst Sausages

Manufacturer	NPY (p.p.m.)	NPi (p.p.m.)
A	0.018	0.06*
	0.014	0.05*
	0.105*	—
	0.02	0.05*
B	0.013	Trace†
C	0.024	N‡
D, E, F	N	N

* Confirmed by GLC-mass spectrometry².

† Less than 0.02 p.p.m.

‡ N, None detected (detection limit, 0.002 p.p.m. for NPY and 0.01 p.p.m. for NPi).

During a recent monitoring survey of meats we observed the consistent occurrence of fairly high levels of NPY in Mettwurst sausages made by certain firms in Canada (Table 1). Similar products from a few other manufacturers were negative. This finding seemed unusual as it was the first reported instance of NPY in sausage.

To study the origin of NPY in these products, the ingredients of this sausage were obtained from the firm "A" (Table 1). Sausages were prepared with and without nitrite, and also with and without the curing mixture. Only the sausages prepared

Table 2 NPy and NPi in the Meat Curing Agent from Manufacturer "A"

No.	Approximate age of the mixture (months)	NPy p.p.m.	NPi p.p.m.
1	3.5	5*†	7*†
2	8	6*	25*
3	6.5	2.5*†	25*†

* Confirmed by GLC-mass spectrometry².

† Confirmed by combined GLC-high resolution (1 in 10,000 with 10% valley definition) mass spectrometry.

with the curing mixture contained NPy, whereas all other samples were negative. Subsequently, it was found that the curing mixture was heavily contaminated with both NPy and another nitrosamine, nitrosopiperidine (NPi). Two other samples of this curing mixture gave similar results (Table 2).

This particular curing mixture was a dry powder mainly consisting of spices (black pepper, paprika, and two other spices), salt, sodium nitrate and sodium nitrite (0.96%). It seemed obvious that some amine components of the spices reacted with nitrite and formed the nitrosamines. Preliminary results indicated that the reaction between spices and nitrite under dry conditions is very slow, and therefore experiments were conducted with aqueous suspensions to determine which of the spices was responsible for the formation of nitrosamines. Results (Table 3) show that both black pepper (*Piper nigrum*) and paprika (*Capsicum annuum*) can react with nitrite to form both NPy and NPi. The other two spices (name withheld to protect the formula) gave negative results. It may be of interest that black pepper predominantly forms NPi, whereas paprika forms mainly NPy. No nitrosamines were formed when the reaction mixtures were analysed immediately after mixing.

It seems that piperidine, pyrrolidine or their precursors in these spices can react with nitrite to form NPy and NPi. Piperidine occurs in black pepper in the form of piperine and chavicine⁹. No report of the occurrence of pyrrolidine in these spices or of piperidine in paprika has been published. Additional work is needed to determine the exact nature of the precursors of these amines.

The sausages were extracted and analysed by a thin-layer chromatographic (TLC) method similar to that described previously^{7,10}. In a few cases, results were confirmed by combined gas-liquid chromatographic (GLC)-mass spectrometric analysis. The nitrosamines from the curing mixture were isolated by vacuum distillation of 2 g of the sample from 50 ml 3 N potassium hydroxide solution. The distillate was made alkaline, extracted with methylene chloride, the extract washed with 1 N hydrochloric acid, concentrated and analysed as mentioned

above. The identity of both NPy and NPi in this curing mixture was confirmed by combined GLC-high resolution mass spectrometry. The mass spectra of the isolated nitrosamines were also identical to that of the authentic standards.

Both NPy and NPi are carcinogenic to laboratory animals¹¹. Although no direct evidence of their carcinogenic effect in man is available, it will be highly desirable to maintain the concentration of these chemicals in food at the lowest possible level. Our results suggest that the practice of premixing certain spices with nitrite in meat curing agents can be hazardous due to the formation of nitrosamines. It is also possible that these spices may react with nitrite in the finished meat products during prolonged storage, processing under heat (for example, canning), or cooking. A full investigation of the problem is urgently needed.

Note added in proof. We have also detected the presence of N-nitrosodimethylamine in this curing agent (samples 1 and 2, Table 2); the level is about 0.85 p.p.m. Preliminary results suggest that it is being formed from the interaction of paprika and nitrite.

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Table 3 Formation of NPy and NPi from the Interactions of Spices and Nitrite

Spice and its concentration*	Sodium nitrite p.p.m.	pH	Incubation period (d)	Nitrosamines formed (μg)	
				NPy	NPi
Black pepper, 4%	2,400	4.5	5	3†	10†
	2,400	6.5	5	0.5	1
	200	4	7	0.4	3†
	200	6.5	7	N	N
	20	2	0.083	N	N
Paprika	2,400	4.5	5	3	1
	200	4	7	0.4	N§
	200	5‡	7	0.3	N
	20	2	0.083	N	N

* The total volume of the reaction mixture was either 50 or 100 ml, and in some cases (pH < 4.5) it contained 5-10 ml of 0.05 M potassium chloride-hydrochloric acid buffer (pH 1.4). Incubation temperature, 35-37° C.

† Confirmed by GLC-mass spectrometry².

‡ Normal pH of the suspension.

§ N= None detected (detection limit, 0.1 μg for NPy and 1 μg for NPi).

Is *Deltatheridium* a Marsupial?

THE family Deltatheridiidae was proposed by Gregory and Simpson¹ to include two late Cretaceous mammals from the Djadokhta Formation of Mongolia (?Coniacian or Santonian²): *Deltatheridium pretrituberculare*, known from two partial skulls and associated lower jaws, and *Deltatheroides cretacicus*, known only by the facial part of a skull with upper dentition. They were believed to occupy a very central phylogenetic position among the eutherian mammals. Van Valen³ included them in the Palaeoryctidae, order Deltatheridia, but one of us (P. M. B.)⁴ has for some time doubted the correctness of these opinions.

The Polish-Mongolian Palaeontological Expeditions^{2,5} have obtained additional and better preserved material of both species, of which a full description is being prepared by Z. K.-J. This material has been collected not only from the Djadokhta Formation but also from the somewhat later ?Middle Campanian⁶ Barun Goyot Formation, and we can now reconsider earlier opinions.

Gregory and Simpson¹ stated that in *Deltatheridium* paracone and metacone are united or very close together; but in

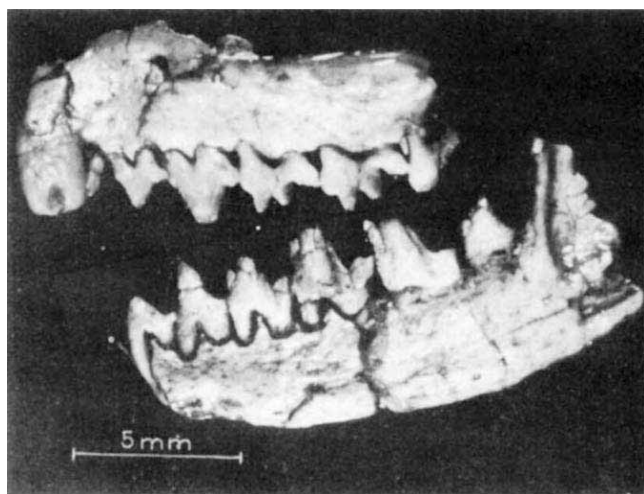


Fig. 1 *Deltatheridium pretrituberculare* Gregory and Simpson, left maxilla with C, P¹⁻³, M¹⁻³ and left mandible with P_{2,3}, M₁₋₄, found in association and separated. Specimen found in the Barun Goyot Formation, locality of Khermeen Tsav II, Mongolia, housed in the Palaeozoological Institute, Polish Academy of Sciences, in Warsaw.

fact the metacone is set well apart from the paracone on the first two molariform teeth and still distinct on the last molar. The last two upper molariform teeth resemble those of *Pappotherium pattersoni* figured by Slaughter⁷.

Lower dentitions show the presence of four molariform teeth. The last of these is a small tooth which has previously been regarded as part of the elongated talonid of M₃, as McKenna *et al.*⁸ have pointed out. On all the molariform teeth the metaconid is less elevated than the paraconid; it is absent in the last molar of *Deltatheridium*. This tooth also lacks a talonid, and functioned only by shearing against the metacrista of the last upper molar. In a mandible from the Djadokhta Formation referred to *Deltatheroides* the last molar is better developed, possessing a metaconid as well as a talonid, and it presumably occluded with an additional upper molar, lost in *Deltatheridium*. *Deltatheroides* is known to have four upper molariform teeth¹, whereas *Deltatheridium* has only three.

To preserve a eutherian dental formula, McKenna *et al.*⁸ interpret the first molariform tooth as a premolar, which they describe as semimolariform. This tooth is very similar to the second molariform tooth, however, differing only in proportions as would be expected from their different positions in the series. There is no sign of any reduction of the metacone of the first molariform tooth in the upper jaw or of the talonid in the lower jaw. No Cretaceous or even Palaeocene eutherian, to our knowledge, shows such a high degree of molarization of P⁴ as this. Moreover, the degree of wear on the two teeth is almost identical (Fig. 1), whereas P⁴ being preceded by a milk tooth is normally less worn than M¹. We must conclude therefore that the two teeth are not P⁴ and M¹ but M¹ and M². It would follow that the molar formula of *Deltatheridium* is $\frac{3}{4}$ and that of *Deltatheroides* is $\frac{4}{4}$.

In both genera there are three premolars in each jaw. The last two are two-rooted and not molariform, as in Didelphidae; in other Cretaceous eutherians P⁴ is always three-rooted and partly molarized. The first premolar is reduced, one-rooted in the upper jaw, two-rooted but obliquely set in the lower jaw. The canines of *Deltatheridium* are large and single rooted. According to Van Valen⁹ there were probably four upper incisors. Thus the dental formula of the Deltatheridiidae is $\frac{24}{9} \frac{1}{1} \frac{3}{3} \frac{4-3}{4}$. This agrees better with the basic marsupial formula $\frac{5}{4} \frac{1}{1} \frac{3}{3} \frac{4}{4}$ than with the eutherian formula $\frac{3}{3} \frac{1}{1} \frac{4}{4} \frac{3}{3}$.

Are the Deltatheridiidae marsupials? Their upper molar patterns, with broad styler shelf and well developed stylocone, resemble some late Cretaceous Didelphidae more than Palaeoryctidae. Reduction of the metaconid is paralleled in *Didelphodon* and Tertiary and Recent carnivorous marsupials, though it also occurs in some creodonts⁹. Loss of M⁴ is very unusual in marsupials. The broad nasals and large jugal of *Deltatheridium* are also found in the eutherian *Kennalestes*². The palate is unperforated.

It is very likely that the ancestral eutherians had four molars like marsupials, and *Deltatheridium* might be a very primitive eutherian still in the process of losing the fourth molar. An undescribed primitive palaeoryctid from the Barun Goyot Formation has five upper and four lower incisors, and the presence of more than three incisors is therefore not diagnostic of a marsupial. The loss of a premolar in Deltatheridiidae might be ascribed to their highly carnivorous specialization.

In view of this uncertainty we prefer to classify the Deltatheridiidae like the Pappotheriidae, as Theria of metatherian-eutherian grade.

There is no reason to believe that the Deltatheridiidae are related to the Maastrichtian-Eocene Palaeoryctidae^{3,10}. As they do not belong to Van Valen's order Deltatheridia this name is inappropriate. Neither do they resemble the Palaeocene Asiatic genera *Hyracolestes* and *Sarcodon*, placed in the family by Szalay and McKenna¹¹.

If they prove to be marsupials, the Deltatheridiidae would be the only Cretaceous marsupials so far found outside America. One-way migration from Asia to North America seems to have occurred in Santonian-Maastrichtian time¹², but migration in the reverse direction at a time before the deposition of the Djadokhta Formation cannot be precluded.

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Reference Abbreviations

ALL abbreviations of references in *Nature* should now conform to the style of the *World List of Scientific Periodicals*, fourth ed. (Butterworth, 1963-65). Authors submitting manuscripts are asked to ensure that the references are written appropriately.

BOOK REVIEWS

Nernst in Context

The World of Walther Nernst: The Rise and Fall of German Science. By K. Mendelssohn. Pp. 191+25 photographs. (Macmillan, London and Basingstoke, June 1973.) £4.95 net.

WHEN John Wilkins wrote *Mathematical Magick* in 1648 the rise of German technology was already foreseen, for in his preface Wilkins noted that "Ramus hath observed, that the reason why Germany hath been so eminent for Mechanical inventions, is because there have been publick Lectures of this kind instituted amongst them, and those not only in the learned languages, but also in the vulgar tongue, for the capacity of every unletter'd ingenious artificer". This was echoed in the middle of the nineteenth century by Lyon Playfair, warning his countrymen that the Continent, particularly Germany, was much ahead in education in science and technology, and urging that we should follow the German example of uniting teaching and research in the universities. This was an argument that Dr Phelps, the Master of Sidney Sussex, actually used against the foundation of the Cavendish Laboratory, appealing to the emotions of his countrymen by declaiming that "A Prussian is a Prussian and an Englishman an Englishman and God forbid it should be otherwise". As Phelps was speaking, Bismark was consolidating the formation of the Second Reich around the discipline of the Prussian army and the intellectual romanticism of Frankfurt. This was the world into which Walther Nernst was born of a Prussian family in 1864.

His life, most deftly sketched by his grandpupil Kurt Mendelssohn, spanned the golden age of German science. When he died in 1943 that age had been shattered by the vilest aberration ever to befall a civilized country, the national socialism of Adolf Hitler.

Mendelssohn provides exactly what one might hope for in an understanding biography of one physicist by another, and at the same time gives a vivid and illuminating picture of Germany, and especially of its academic life, before and after the First World War. The key-points of Nernst's physics are set with clarity in their historical context and the

theme of Nernst's life is interwoven with those of his near-contemporaries among the great German physicists including Boltzmann, Born, Einstein, Hahn, Heisenberg, Helmholtz, Hertz, von Laue, Paschen, Pauli, Planck, Schrödinger, Sommerfeld, Stern, and Wien. The result is a scintillating cavalcade of vital physics and human anecdote against a penetratingly sketched background of the fortunes and misfortunes of the Second and Third Reich.

Inevitably, the German attitude towards the Jews figures largely in the book, if only because this led to the break-up of German science after 1933. The Jews had been emancipated in Prussia in 1812 and, despite some prejudice, had come to occupy high places in the Second Reich; Kaiser Wilhelm the Second in fact so much disapproved of anti-Semitism that he dismissed its main protagonist, Adolf Stoecker, from his court, and it was natural for Jews like Rathenau and Haber to be called in to provide vital services in the First World War. That the Jews as a race were outstandingly gifted can hardly be denied by any present-day anti-racist for, as Mendelssohn points out, although they made up about only one per cent of the population of Germany, they won one-third of its Nobel Prizes. How then did such a gifted people come to be so terribly ill-treated? And how could two Nobel Prize winners, Stark and Lenard, reject relativity because Einstein was a Jew?

After World War II, I was the guest of a gathering of many German generals, Kesselring and Galland included, in Munich. An English friend, sensing that I might be overwhelmed with their hospitality, took me off one afternoon to see Dachau. Even ten years after the crematoria were cold it was a sombre experience. Afterwards, back in the Hofbräu when we were pledging eternal friendship, I told the generals that I had just been to Dachau, and asked them what they were going to do to stop it ever happening again. Some of them argued that they had had no knowledge of the concentration camps until after the War, and that they were deeply shocked to find how much they could all have been so misled by

one man. One general, however, did attempt to answer my question. He said that while it was true that most of them had known nothing about the concentration camps, they must admit that the camps were there, and he for one could not understand how they could possibly have come about. And, he added, because he could not understand the process by which they had happened, he could not see how the Germans could guarantee that they could never happen again. His answer, at least, was honest.

Mendelssohn expresses warm appreciation for what was done in Britain and America to offer refuge to those scientists who could get out of Germany after 1933. At the same time he recalls that there were some such as Hahn, von Laue, and Carl Bosch, all men of the highest honour, who stayed in Germany and struggled at some risk to their own lives to keep German science free from Nazi dogma through the height of the purges. Mendelssohn includes an appreciative epilogue about Nernst's best-known pupil, F. A. Lindemann (Lord Cherwell), who incidentally first met Henry Tizard when they were both research students in Nernst's laboratory.

Necessarily, in a short book, Mendelssohn has had to paint some of the background with a broad brush, and the strokes occasionally falter. There is a photograph of Nernst lecturing in his characteristic fashion (Mendelssohn records that Nernst had "toyed with the idea of becoming an actor himself and he realized this ambition to some extent by wearing throughout his life the mask of a trusting and credulous little man. His favourite expression of innocent astonishment could be underlined by a twitch of the nose which removed the pince-nez") which the caption dates as 1926; but Nernst has written on the blackboard the name "Lord Rutherford", who was not ennobled until 1931.

Such trivia, however, do not detract from the genuineness of the book, which gives an illuminating portrait of Nernst's character and of his achievement in the Third Law of Thermodynamics. It is a rare kind of book, and of its kind it is outstandingly good.

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Coli and Coliphage

Experiments in Molecular Genetics. By Jeffrey H. Miller. Pp. xv+466. (Cold Spring Harbor Laboratory: Cold Spring Harbor, New York, 1972.)

MANY of the exciting advances in modern biology were dependent on the study of genetic variants: genetics has become a very powerful biochemical tool. Because of its pre-eminent suitability for both genetical and biochemical investigation, *Escherichia coli* undoubtedly remains the organism of choice for the elucidation of many fundamental biological principles. Jeffrey Miller's laboratory manual, growing out of the famous bacterial genetics course at Cold Spring Harbor, deals exclusively and comprehensively with the molecular genetics of *E. coli* and its phages.

The presentation begins at the simplest level by introducing basic techniques such as dilution methods, sterile plating and viable cell counts. The subject matter gradually increases in complexity, finally covering such recent experiments as the purification and properties of repressor proteins and cell-free enzyme synthesis. Each of the nine major sections is introduced with a well-referenced discussion of the background theory and general value of a particular experimental approach, and ends with a series of questions intended to promote further thinking. The accounts of the many individual experiments are preceded by short discussions of the rationale and strategy. The very detailed experimental protocols include lists of chemicals and apparatus required for each exercise.

One of the many strengths of the book is the profusion of advice on such matters, for example, as the choice of starting strain, the idiosyncrasies of particular mutants or the action to take on spillage of a noxious chemical.

Jeffrey Miller has succeeded in producing a superb laboratory manual, which reveals much of the lore of *E. coli* genetics. The volume should obviously find constant use in bacterial genetics laboratories for many years. The strain lists obtainable with the manual will be particularly useful to teachers who do not have access to a good strain collection.

W. J. BRAMMAR

Cybernetics

Fundamentals of Cybernetics. By A. Ya. Lerner. Translated from Russian by E. Gros. Translation edited by F. H. George. Pp. x+294. (Chapman and Hall: London, August 1972.) £6.

THIS book originally appeared in the USSR as long ago as 1967: it therefore, *de facto*, cannot—as asserted by the

editor of this English translation—provide “a good insight into the contemporary Russian approach to cybernetics”. In fact, the whole face of Soviet cybernetics has changed radically since the original publication of this book, principally as a result of the efforts of the outstanding groups of cyberneticians working at the Institute of Control Sciences in Moscow and at the Institute of Cybernetics in Kiev. Even allowing for this fact, however, it is unlikely that this book will be very useful for its intended readership: for, in writing this book, Professor Lerner “wished particularly to assist people with inadequate mathematical knowledge and without the necessary time to study the works of Wiener, Shannon, Andronov, Kolmogorov and others, but who, in spite of this, wanted to study the methods of solving cybernetic problems”. It is hard to see how such people will benefit in this way by reading the nineteen very brief chapters of the book which contain cursory discussions of such vast topics as automatic control, optimal control, automata, computers, adaptation, games, learning, large systems, operational control, the brain, organized systems, man and machine, and the future prospects of cybernetics. Indeed, it is ironical that the text which still provides the best introduction to the fundamentals of cybernetics is advertised on the jacket of Professor Lerner's book: this, of course, is *An Introduction to Cybernetics* by W. Ross Ashby which—as Stafford Beer has remarked—“is an education in itself (which) demonstrates that you can change your life quietly as well as dramatically”. BRIAN PORTER

Organic Atlas

Atlas of Spectral Data and Physical Constants for Organic Compounds. Edited by Jeanette G. Grasselli. Pp. 1,697. (CRC Press: Cleveland, Ohio; Blackwell: Oxford, 1973.) £50.

THE Chemical Rubber Company's *Handbooks of Chemistry and Physics* (HBCP), now in their fifty-third edition, are familiar and most useful pieces of laboratory equipment. In the past few years sixteen other *Handbooks*, three *Manuals*, a set of *Tables*, and now this *Atlas*, have appeared under the same imprint.

The volume is organized in three sections. Section A is introductory, dealing under separate headings with the four spectroscopic techniques; infrared, ultraviolet, nuclear magnetic resonance, and mass. Much of the material, including useful infrared correlation charts, is reprinted from HBCP and will doubtless appear again in the forthcoming *Handbook of Spectroscopy*.

Section B contains the “Master Data Table”, preceded by a synonym directory; in spite of the title “Atlas” the data are all in tabulated numerical form. About 8,000 compounds are listed; the large majority of these appeared in HBCP (fifty-second edition) and they are tabulated similarly here, with the additional spectra data and the Wiswesser line notation (WLN) code. All the spectroscopic data, with the exception of some of the ultraviolet, come from published collections. There are infrared data for about 5,550 compounds, of which almost two-thirds come from the Sadtler collections, much of the rest from the Coblenz Society (also Sadtler), and a few from the DMS, API and NBS collections. Compounds for which ultraviolet data are given number about 4,800. Data for about half of these appeared without references to source in HBCP and are listed again, log ϵ values having been converted, or reconverted, to ϵ values, and remain without references. As in HBCP, the so-called references in the first column are to Beilstein or Elsevier and are therefore of little use. Of the remaining ultraviolet data, there are literature references for about 450 compounds, and the rest, about 1,950, are from the Sadtler collection. The NMR data are the least comprehensive; of less than 2,600 compounds Sadtler contribute data for 2,250, the rest being Varian, and the absence of any assignments diminishes considerably the value of this material. Of 3,050 mass spectra, 870 are Aldermaston and the rest are from the Wiley collections.

Section C comprises the indexes. After formula and physical constant (m.p. and b.p.) indexes, a large subsection is devoted to the WLN system, including an extensive permuted index designed to correlate data from compounds with common functional groups or substructures. Then follow comprehensive indexes for each of the four spectroscopic techniques, based upon wavelengths (frequencies, chemical shifts, mass numbers) and intensities of the most prominent features. Except for the ultraviolet index these also list WLN codes and their permuted abbreviations which are called, somewhat grotesquely, “Eyeball”.

The WLN index system works surprisingly well even for somebody quite unfamiliar with it; it is easy to pick out, for example, all the phenyl ethers or all the α -ketoesters listed, and, before referring to the Master Data Table, to see at a glance which of these have, say, infrared or mass spectra. The value of the Tables which list bands in order of wavelength is less certain. They are too vulnerable to the effects of converting rounded-off

wavenumbers to rounded-up wavelengths, and also to the idiosyncracies of the compiler-curve reader. An unexpected check of consistency in this last respect was obtained from two instances in the Master Data Table where the same compound had been entered twice. The result was not altogether encouraging, and this brings me to the question of accuracy. The larger the collection of data, the less chance there is of a systematic correction being made, and each re-tabulation will retain the old errors and almost certainly introduce new ones. Both occur here, though it is difficult to say on what scale. In a familiar group of eight isomeric compounds in the Master Data Table, I found five numerical errors in the material I was able to check. Two were carried over from *HBCP* and three were new introductions; two of these errors led to misplacements in other tables. It is surprising, too, to find the compound 'Antabue', together with several related disulphides, indexed as a distibine derivative, especially as the single genuine distibine which headed the misleading list in *HBCP* does not appear in the *Atlas*.

If these criticisms seem trivial or carping, the accuracy with which the data are reproduced is of the first importance in a volume such as this. The choice of sources is another matter. In most of the large spectroscopic collections the quality is adequate to good, but the physical constants and many of the ultraviolet data are taken from miscellaneous and sometimes obsolete publications in a manner which is quite unpredictable, since it reflects the piecemeal manner in which the *HBCP* collection has been built up over the years. As a volume it is both expensive and unwieldy (5 kg!), but it is probably a worthwhile acquisition for many large research or industrial laboratories; the indexing system, its real *raison d'être*, has many merits and, as far as I know, no parallel. If the data could be properly checked and updated the *Atlas* might almost justify the comical mutual adulation of its three prefaces.

E. A. JOHNSON

Humus Chemistry

Humic Substances in the Environment. By M. Schnitzer and S. U. Khan. Pp. vii+327. (Marcel Dekker: New York, November 1972.) \$19.50. £9.30.

THIS book would have been more accurately titled "The Chemistry of Humic Substances" and one suspects that the chosen title was designed to court the interest of some environmentalists other than those schooled in chemistry. Such will find morsels to

interest them in the first and last chapters but the strong meat of the work lies in the intervening pages, which are principally devoted to chemical aspects of the extraction, composition, and properties of humic substances. Surprisingly, the first brief introductory chapter makes no mention of the vast deposits of peat that constitute the main bulk of the humus compounds of the natural environment in the northern hemisphere.

In the following six chapters, however, the authors have compiled an excellent detailed systematic account of the physico-chemical properties and composition of humic substances from a wealth of information that has hitherto been scattered through various journals, reviews and diverse publications. Chapter 2 covers the extraction, fractionation and purification of humic substances and leads on logically to one dealing with chemical and another with physical methods for their characterization, followed by a fifth chapter devoted to the chemical structure of these compounds. The researches of Dr Schnitzer and his co-workers over the past three decades have contributed very significantly to the story, so it is natural that these are well covered—but not to the neglect of other contributors. Chapters 6 and 7 comprise very useful reviews of the reactions of humic substances with metal ions, hydrous oxides and clay minerals, again with the emphasis on laboratory studies though implications are drawn regarding the contributions of humus substances to the overall properties of natural soils.

The last chapter deals briefly with the reactions of humic compounds with synthetic organic compounds that are increasingly being added to soils for the protection of crops from pests, diseases and weeds, and with nitrogen containing substances such as fertilizer urea. Some attention is also given to the physiological effects of humus compounds on the growth of higher plants. The main topics covered in this last chapter are dealt with in greater detail in other texts of the same series of publications on soils and the environment.

Those engaged in serious research on humic substances will be grateful to the authors for providing a valuable source book of information and making a brave attempt to present a coherent story even though it adheres rather firmly to an examination of the composition and properties of the traditional "fulvic" and "humic" acid fractions without defining the "purity" of these materials adequately in some cases.

The price is high for a work of this kind. Those enthusiasts among advanced students, lecturers and professional researchers who do invest in a

copy will not be disappointed: others will undoubtedly recommend it for their libraries.

J. TINSLEY

Chromosomes in Cytology

General Cytogenetics. By J. Sybenga. Pp. xiii+359. (North Holland: Amsterdam and London, 1972.) Dfl. 70; \$22.

CYTOGENETICS originated as a purely descriptive science and morphology, with a strongly quantitative bias, continues to be an important component. Having become allied with embryology, physiology, chemistry and physics, the subject has, however, developed into a wide-ranging experimental discipline impossible to cover at other than an introductory level in one relatively slim volume. The author's emphasis of classical topics gives a somewhat distorted picture of the current state of the field, and in view of the existence of several good texts covering basic cytogenetics the need for a book of this nature is questionable.

The book's main contribution lies in a comprehensive treatment of recombination, ranging from monofactorial segregation to gene conversion and incorporating data from prokaryotes and eukaryotes. Extensive coverage is given to structural and numerical chromosome variation and a chapter on genetic chromosome maps economically compiles information from viruses to higher organisms. These topics, occupying some two-thirds of the text, are concisely surveyed and successfully illustrate the relationship between cytological observation and genetic thought. The rest of the book is less satisfactory. Specialized chromosomes and deviant cytogenetic systems are summarily described. Least successful is the chapter, entitled "Background", which deals largely with current topics related to molecular cytology. Because of the variety and highly condensed form of the information, the reader is confronted with an apparently random catalogue of facts, more irritating and disturbing than informative. This important section would have profited greatly had one chapter been devoted specifically to methods, and the terminology appended in the form of a glossary.

The book is intended as an undergraduate text. Its specialization and variable level of information probably render it unsuitable for most courses and, more important, no attempt seems to have been made to lead the student from established fact to a consideration of questions which remain unanswered. While the author's preoccupation with terminology and classification makes the text somewhat tedious, the organization into subheadings facilitates

access to factual data and the volume should prove a convenient reference work. A minor criticism relates to the numerous grammatical errors, spelling mistakes and misprints. The book is clearly printed on excellent paper and is well and fully illustrated.

I. HARTMANN-GOLDSTEIN

Haemophilia

Haemophilia. Edited by F. Ala and K. W. E. Denson. (Proceedings of the VII Congress of the World Federation of Haemophilia, Tehran, May 1971.) Pp. xviii+308. (Excerpta Medica: Amsterdam, 1973.) Dfl. 72; \$22.50.

THIS book shows yet again how the elegant (and therefore slow) publication of congress proceedings defeats its own object. The Seventh Congress of the World Federation of Haemophilia was held in Tehran in May 1971, and it has therefore taken two years for the proceedings to appear. During this time there has been much activity in the haemophilia field, particularly on the relation between the antigenic, coagulant and other functional activities of antihæmophilic factor. This work has proved to be of great importance in relation to the pathogenesis of haemophilia and von Willebrand's disease, and a book with this title therefore now looks very bare with such scant reference as it necessarily contains to this aspect of the disease.

The book is divided into seven sections, of which the first, on the regulation of factor VIII synthesis, is probably the most valuable. The short section on genetic variants of coagulation factors is now inevitably somewhat out of date and the heading "pathophysiology of haemostasis" gives a quite erroneous impression of the content of the next four assorted papers. There follows a section on blood transfusion and plasma fractionation, which includes papers on the organization of blood transfusion services and on the Australia antigen as well as the preparation of cryoprecipitate for the treatment of haemophilia, but omits consideration of other methods of fractionation of antihæmophilic factor. The remaining three sections are on orthopaedic, dental and other aspects of the treatment of haemophilia.

There is little of value in this volume which has not been published elsewhere in greater detail, and despite the useful series of short reviews which it contains—notably those by Ingram, Dodds, Denson and Blombäck—it is difficult now to recommend it. Had elegance of production been sacrificed to speedy publication, it might have had more value for coagulationists who were unable to attend the congress.

R. M. HARDISTY

The Numbers Game

Data Analysis in Biochemistry and Biophysics. By M. E. Magar. Pp. xvii+497. (Academic: New York and London, December 1972.) \$24.

REPUTATIONS have been made by casting the equations describing theoretical models into linear form so that interesting parameters can be readily extracted from experimental data. Faced with more complicated theories, most physical biochemists have been reduced to trial and error methods and it is regrettably rare to find adequate attention paid to statistical errors.

The purport of this book is to describe mathematical methods which enable parameters to be extracted from experimental data (with, maybe, the use of computers) using models of any complexity and with the maximum reliability. It is not a manual of methods with easy-to-use recipes; nor is it recommended to experimentalists with no head for mathematics—for Clarendon type and multiple suffixes are liberally sprinkled on its pages.

The book is divided into two parts. In the first theoretical section the mathematical methods are outlined. No doubt with the mathematically naive reader in mind, the sections on matrices, analysis and statistics start from first principles. In these chapters a chatty style helps the reader to an intuitive understanding and the more difficult proofs are left out. Unfortunately the galloping pace makes me doubt whether this naive reader will in fact be led to numeracy by Dr Magar. Nevertheless this section culminates in a useful chapter on function minimization; the topics covered, though all to be found in books on numerical analysis, are not as widely known as they might be to physical biochemists. Thus, beside standard treatments of least squares techniques for linear and non-linear systems, Chebyshev minimization and linear programming are usefully described.

In the second "applied" part of the book, the experimentalist is reassured that all this mathematics is germane to his interests. In a series of chapters on spectroscopic properties of nucleic acids and proteins, kinetics, ligand binding and aggregating systems in the ultracentrifuge and elsewhere, the use of the mathematical techniques is illustrated. There are better and more up to date reviews on all of these topics and little attempt is made to assess the models described or discuss their physical basis. The physical biochemist may find his problem solved in these chapters or a solution may be suggested to him; but he will need a mastery of the first half of the book.

I was dismayed by the large number of misprints or worse and by the fact

that my copy started to fall to pieces sooner than I would have expected for the price.

E. G. RICHARDS

Breaking Ice

Studies in Ice Physics and Ice Engineering. Edited by G. N. Yakovlev. Translated from Russian. Pp. v+192. (Israel Program for Scientific Translations: Jerusalem; John Wiley: Chichester, March 1973.) £7.50.

OBSERVING that this book has an editor, but no authors, one might think that a series of chapters by specialist authorities had been welded into a review covering most aspects of ice physics and ice engineering. Not so. This is Volume 300 of the *Proceedings of the Arctic and Antarctic Scientific Research Institute in Leningrad*, and I think the title, or a subtitle, ought to make that clear. Since Volumes 299 and 301 may, or may not, be translated by the Israel Program it would be helpful to know what organizations in the English-speaking world are consulted in the making of their choice for translation.

The individual research papers which make up this volume are not so diverse, however, as might be found in many a scientific journal: without exception they refer to sea ice, with occasional reference to lake ice and river ice, and the slant is invariably towards icebreaker operations. No physicist should be offended therefore if I suggest that "Ice Physics" in the title is misleading.

One paper describes the laboratory facilities of the Arctic and Antarctic Institute in official-report-style language. There is, however, some scientific discussion of the interesting problem of the factors to be maintained in making scale-model tests of an icebreaker in a laboratory pool.

One is never quite sure about misprints and mistranslations. Were the measurements of ice pressures on page 4 really made in February 1923? Since the translator has transliterated the abbreviations for units (M.T./m² on the same page), should he give us his own guess as to what they really are? In general, the translator uses ponderous literal phrases: "establishment of isothermy", "homothermal", "weight-type forces", "... concrete, the water-impermeability of which was ensured by several layers of hydro-insulation"—perhaps these help preserve the Russian flavour. It was never in any real danger.

This book will be of some interest and use to sea ice specialists, especially those concerned with breaking it. Beyond that, to meteorology, climatology, permafrost, hydrology, or ice physics, I doubt if there is any application.

S. EVANS

CORRESPONDENCE

Algebra of Certainty

SIR,—Under the heading "Value of a Hypothesis" your correspondent (*Nature*, 244, 329; 1973) discusses Sturrock's attempt to form strong inferences from a number of, in themselves, inconclusive observations. He says: "One thing to be learned from Sturrock, however, is that, even if each available item is inconclusive in itself, the resultant effect of several items may give almost completely convincing support for one solution."

This approach to certainty has been used by others, notably Cardinal Newman, as recorded in the well-known verses:

"There was a grave prelate named
Newman
Whose soul was sufficient for two
men;
He said: 'In sooth,
Three doubts make a truth,'
Which he thereupon proved with
acumen."

Unfortunately, Sturrock is harder to rhyme.

Yours faithfully,

H. W. DAVENPORT

*The University of Michigan Medical School,
Department of Physiology,
Medical Science Building,
Ann Arbor, Michigan 48104*

Hump Back Salmon

SIR,—In the late 1950s the Russians undertook extensive plantings of the Pacific hump back salmon (*Oncorhynchus gorbuscha*, Walbaum) in rivers on the Kola Peninsula entering the Barents Sea and recaptures were made within two years, apart from Russia itself, in Norway, Iceland and the United Kingdom. At that time no recaptures were reported from Ireland.

On August 14 a male hump back salmon, measuring 60 cm and weighing 2 kg, was taken by an angler from the River Moy in the north-west of Ireland. This is the first specimen of a hump back salmon to be recorded from Irish waters, all previous reports having related to deformed members of the Atlantic salmon (*Salmo salar*).

Yours faithfully,

A. E. J. WENT

*Department of Agriculture and Fisheries, Fisheries Division,
3 Cathal Brugha Street, Dublin 1*

A Question of Growth

SIR,—I am writing this on the off chance that it might fill some minuscule gap in research, or suggest some useful line of enquiry.

For the past ten years or so, I have spent my summer holidays in Interlaken (Bernese Oberland), staying two to three weeks. On every visit, I have found that my finger nails and my hair grow at less than half the rate they grow in London, where I live. The growth rate slows down almost immediately on my arrival, and continues until I return to London, when it starts up again at the usual rate.

Interlaken is at 1,860 feet, and its very pure water is taken from the Saxeten valley, to the south-west.

I am about 6 feet tall, and rather fat, and am mostly a vegetarian. I drink sparsely in London, and a good deal in Switzerland; but otherwise my habits seem to have little to do with the matter. I am now 64 years old.

I have mentioned this peculiarity to a number of people but no one can explain it; but it has always struck me as very odd indeed. Perhaps your readers number someone who has made a study of nail and hair growth, and who could either enlighten me, or use me as a guinea-pig.

Yours faithfully,

CHARLES H. GIBBS-SMITH

*Residence C,
Victoria and Albert Museum,
London SW7*

Announcements

University News

Dr D. M. Smith, University of New England, has been appointed to the **Chair of Geography** at Queen Mary College.

Dr B. T. Donovan, Institute of Psychiatry, has been given the title of **Professor of Neuroendocrinology** at the University of London.

Dr D. W. Moore, Imperial College, has been given the title of **Professor of Applied Mathematics** at the University of London.

Dr M. L. Rutter, Institute of Psychiatry, has been appointed to the **Chair of Child Psychiatry** at the University of London.

Appointments

Dr R. G. Baker, British Steel Corporation, has been appointed **Superintendent of the Division of Materials Applications** at the National Physical Laboratory.

Miscellaneous

Dr Leo Goldberg, Kitt Peak Observatory, has been elected **President** of the **World Astronomical Body**.

Mr K. C. G. Heath, Anglo American Corporation, has been elected **President** of the **Institution of Mining and Metallurgy**.

Erratum

In the article "Origin of Bright Spots in High Resolution Dark Field Electron Microscopy" by G. J. Brakenhoff (*Nature*, 243, 512; 1973) line 7 of paragraph 2 should read "The overfocus distance of the dark field bright spots is 350 ± 80 nm with respect to the geometrical image plane", and the last line of paragraph 2 should read "The scatter angles for electrons to contribute to the dark field image are in between 0.001 and 0.012 radians". Paragraph 6 should read "Third, the bright points are found at overfocus in relation to the geometrical focus. Then, a plane is imaged that is, relative to the direction of travel behind the object, just where according to the present model one would expect the interference maxima".

International Meetings

October 1–3, **International Conference on Land for Waste Management** (M. K. Ward, Executive Secretary, International Conference on Land for Waste Management, National Research Council, Ottawa, K1A 0R6, Canada).

October 2–4, **Industry and Effluent** (CDRA, 29 St James's Street, London SW1A 1HB).

October 2–6, **Symposium on Remote Sensing in Oceanography** (Dr J. P. Latham, Florida Atlantic University, Boca Raton, FL 33432).

October 3, **A Joint Meeting of the Food Group and the Microbiology, Fermentation and Enzyme Technology Group** (Mr D. Hicks, Honorary Secretary, Food Group, Chief Research Manager (Food and Drink), Beecham Products Ltd., Beecham House Annexe, Great West Road, Brentford, Middlesex).

October 3, **Conference on the North East's Advantages for the Chemical Industry** (N. T. Shepherd, The Institution of Chemical Engineers, 16 Belgrave Square, London SW1X 8PT).

October 5, **The Autumn Meeting and Annual General Meeting of the Bone and Tooth Society** (The Secretary, Bone and Tooth Society, London).

October 5-6, **The First Meeting of the Southeastern Cancer Research Association** (Dr Wayne E. Criss, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville, Florida 32601).

October 8-12, **First International Conference on Driver Behaviour** (Mr T. E. A. Benjamin, Secretary General, International Drivers' Behaviour Research Association, Room 9 C27, 10 quai Paul Doumer, F-92 Courbevoie, France).

October 8-14, **The Third World Congress of Underwater Activities** (Bernard Eaton, Chairman, Publicity Committee, Grosvenor House, Park Lane, London W1).

October 8-15, **The 24th International Astronautical Congress** (IAF Secretariat, 250 Rue Saint-Jacques, 75005 Paris, France).

October 9, **Risks and Benefits in Medical Uses of Ionizing Radiations** (Professor J. H. Martin, Department of Medical Biophysics, The University, Dundee DD1 4HN, Scotland).

October 12-13, **The 6th Symposium of the International Society for Research in Stereoencephalotomy** (Professor H. Narabayashi, Neurology Department, Juntendo University, Bunkyo, Tokyo).

October 15-17, **Symposium on Energy Resources** (The Executive Secretary, The Royal Society of Canada, 395 Wellington, Ottawa, K1A 0N4).

October 15-18, **The Second International Estuarine Research Conference** (Austin B. Williams, Systematics Laboratory, National Marine Fisheries Service, US National Museum, 10th and Constitution Avenue, N.W., Washington DC 20560).

October 18, **A Symposium in honour of Sir C. Maurice Yonge, F.R.S., and Dr Nellie B. Eales** (Honorary Secretary, Malacological Society, Dr Joyce Rigby, Biology Department, Queen Elizabeth College, Campden Hill, London W8).

October 19, **Structure and Function of Chloroplasts** (Dr J. Barber, Botany Department, Imperial College, London SW7).

October 21-25, **The 36th ASIS Annual Meeting** (The Secretary, American Society for Information Science, 1140 Connecticut Avenue, NW, Suite 804, Washington DC 20036).

October 22-26, **Effects of Neutron Irradiation upon Cell Function** (National Authorities for Atomic Energy Matters).

October 22-27, **Planning for the Future** (Director of Information, International Planned Parenthood Federation, 18-20 Lower Regent Street, London SW1Y 4PW).

October 24-25, **Auger Electron Spectroscopy—Materials Applications and Quantification** (The Meetings Officer, The Institute of Physics, 47 Belgrave Square, London SW1X 8QX).

October 24-25, **International Symposium on Gonorrhoea** (Mrs Jean R. Renaud, Symposium Secretary, Room 1-5, Food and Drug Building, Health Protection Branch, National Health and Welfare, Tunney's Pasture, Ottawa, Ontario K1A 0L2).

October 24-25, **Environmental Chemistry: Know-How and Chemicals** (i.b./c.c. Ad-

ministration, Nieuwelaan 65, B-1820 Strombeek, Belgium).

October 24-26, **Materials in Packaging** (I. B. Smith, Department of Polymer Science and Technology, Brunel University, Kingston Lane, Uxbridge, Middlesex).

October 25, **Motorways and the Biologist** (R. K. Tabor, Symposium Organizer, Faculty of Science, Department of Applied Biology, NE London Polytechnic, Romford Road, London E15 4LZ).

October 25-28, **The 3rd International Symposium on Atherosclerosis** (Kongressgesellschaft für ärztliche Fortbildung e.V., D 1 Berlin 41, Wrangelstrasse 11-12, Germany).

October 28-31, **The 44th Annual Meeting of the Society of Rheology** (H. P. Schreiber, Department of Chemistry, McGill University, PO Box 6070, Montreal, Canada).

October 29-31, **Conference on Electrical Insulation and Dielectric Phenomena** (Dr Nelson T. Grisamore, NAS, 210i Constitution Avenue, Washington DC 20418).

October 29-November 2, **Standard Reference Materials and Meaningful Measurements** (Office of Standard Reference Materials, SRM Symposium, National Bureau of Standards, Washington DC 20234).

October 30, **New Directions in Transport** (Mr John Barrick, A.L.A., The Library, Royal Town Planning Institute, 26 Portland Place, London W1N 4BE).

October 31-November 3, **Annual Meeting of the Division of Plasma Physics** (J. L. Johnson, Program Chairman, Princeton University, Plasma Physics Laboratory, James Forrestal Campus, PO Box 451, Princeton, NJ 08540).

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